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TRAUMATIC INTRACEREBRAL HEMORRHAGE

WITH PARTICULAR REFERENCE TO ITS PATHOGENESIS AND ITS RELATION TO "DELAYED TRAUMATIC APOPLEXY"

CYRIL B. COURVILLE, M.D.

AND

OLOV A. BLOMQUIST, M.D.

LOS ANGELES

To those familiar with the effects of trauma on the brain and its envelopes, the importance of the mechanism by which the injury is produced in interpreting the pathologic picture is quite evident. Each type of injury is now known to produce its own characteristic train of lesions. The appalling increase in craniocerebral injuries consequent to traffic accidents has brought into prominence a number of effects which appear to be the direct consequence of striking of a stationary or relatively stationary object by the head in motion. These effects have been long described as *coup-contrecoup* effects. One of the lesions belonging to this group which to date has not been given any selective attention is gross hemorrhage into the cerebral substance—traumatic intracerebral hemorrhage.

In 1891, Bollinger described 4 cases in which death occurred rather suddenly from twelve to fifty days after an injury to the head and proved at autopsy to have been due to hemorrhage into the ventricles or the brain substance. Since that time considerable attention has been given, particularly in the contemporary French and German literature, to a syndrome which has come to be known as "delayed traumatic apoplexy," in the support of which several involved theories have been elaborated. The importance of determining the truth or falsity of this assumption from a medicolegal standpoint, if for no other reason, is clearly evident. Should a patient or his dependents receive compensation or damages as a consequence of an apoplectic stroke which occurs, for example, one month after a cranial injury? Is there evidence to support the assumption that such a condition as delayed traumatic apoplexy actually exists? If so, is there any relation between this condition and gross intracerebral hemorrhage which occurs shortly after an injury to the head?

From the Department of Neurology, College of Medical Evangelists, and the Cajal Laboratory of Neuropathology, Los Angeles County Hospital.

It is the object of this contribution to report our observations in a series of 38 cases of gross hemorrhage into the cerebral substance which followed injury to the head. We propose to discuss the mechanism of production of traumatic intracerebral hemorrhage, to determine its various pathologic types, to present its gross characteristics and to note its ultimate effect on the brain. With the resultant findings to use as criteria, the matter of delayed traumatic apoplexy will then be scrutinized.

MATERIAL AND METHODS

For this study the records of a series of 439 cases of fatal craniocerebral injury have been studied. In these cases the patient was examined clinically in the neurosurgical service at the Los Angeles County Hospital. The autopsies were performed by the coroner's surgeons, Dr. A. F. Wagner and Dr. John H. Schaefer, who furnished one of us (Courville) with records of their observations and permitted him to make a personal study of the intracranial lesions.

In order to determine the mechanism by which the various lesions were produced, an effort has been made to determine from the hospital notes and other records how the injuries were sustained. Attention was given to the points of application of force to the head as well as to the location of intracerebral injuries. Correlation was also made with the roentgen findings during life and with the location and type of the fracture of the skull observed at autopsy.

In this series of 439 cases, 36 cases of gross hemorrhage into the brain were discovered. Two additional cases were found in the records of the Cajal Laboratory from other sources. We have excluded a number of cases in which the hemorrhages were relatively small, that is, in which the clot was smaller than a cherry. This was done to establish some sort of criterion as to the size of the clot, although even in these excluded cases the mechanism was found to be the same as in the case of the larger hemorrhages. To note any possible effects of injury on the blood vessels or the nerve tissue in the region of the basal ganglions and particularly the internal capsule, the brains in a series of over 80 additional cases of old injury of the brain, sustained between three months and twenty years before death, which resulted from some other cause have also been studied. It is from this list of cases that 2 of the 38 cases of traumatic intracerebral hemorrhage have been taken to show the delayed effects of such hemorrhage.

MECHANISM OF CEREBRAL INJURY

In another connection,[1] reference has been made to the mechanism by which traumatic lesions of the brain are produced. Such lesions

1. Courville, C. B.: Pathology of the Central Nervous System: A Study Based upon a Survey of Lesions Found in a Series of Fifteen Thousand Autopsies, Mountain View, Calif., Pacific Press Publishing Association, 1937, pp. 181 and 182.

may be the result of a direct or an indirect injury; those due to the former mechanism are most common and of greatest importance. Indirect injury, such as falls on the feet or buttocks or blows to the chin, rarely produce gross cerebral lesions. On the other hand, direct injuries may produce cerebral lesions by (1) compression of the head by some relatively unyielding object, (2) striking of the head by an object in motion and (3) striking of a relatively immobile, solid object by the head in motion. In this last group are to be found injuries sustained in traffic accidents or falls.

In traffic accidents, whether injuries are the result of collision between two automobiles or between an automobile and some relatively stationary object or whether a pedestrian is struck by an automobile, the craniocerebral damage is sustained while the head is in motion. The resultant lesions, namely, certain types of subdural and subarachnoid hemorrhage, contusions of the brain and petechial and gross hemorrhages into the brain substance, are the result of this peculiar mechanism and are designated as *coup-contrecoup* lesions. At the same time, as a result of falls or forcible projection against some relatively immobile object, there may also be sustained direct injuries at the point of impact should the head strike a small object with sufficient force to cause local injuries to the skull.

CLASSIFICATION OF TRAUMATIC INTRACEREBRAL HEMORRHAGE

On the basis of the mechanism by which the lesion is produced, a study of our cases disclosed two separate types of traumatic intracerebral hemorrhage. The first type occurs as a consequence of direct injury to the skull and is usually associated with a compound fracture. The second type of hemorrhage is that which is the result of a *coup-contrecoup* mechanism. These hemorrhages in turn may be adjacent, consequent to a local contusion, or may occur independently within the cerebral centrum.

Traumatic Intracerebral Hemorrhage Due to Direct Injury.—It is natural to expect that serious injuries to cerebral or cerebellar vessels by fragments of skull or indriven foreign bodies will be followed by more or less extensive hemorrhage. Whether or not such an injury to the skull is followed by severe bleeding depends entirely on the extent of laceration of the brain and the proximity of the lesion to one of the major arteries or veins. In our experience (with relatively few cases) compound depressed fractures over the area supplied by the middle cerebral artery and its major branches are most apt to be followed by gross hemorrhage.

The immediate effect of an indriven fragment of bone or foreign body is laceration of the brain, the extent of which is naturally limited by the margins of the depressed area and its depth by the extent of

penetration of the fragments from the skull or the associated foreign body. In addition to direct laceration of the brain substance by fragments of the skull, gross effusion of blood into the cerebral substance further results in excavation of a cavity in the brain (fig. 1). If the patient survives the injury, the clot absorbs, and a more or less sharply outlined cavity remains directly beneath the defect in the skull. This cavity may extend into the lateral ventricle. It does not present the serious scarring and deformity with adhesion to the dura which accompany a depressed fracture with laceration of the brain without serious hemorrhage.

We have observed but 3 cases which would answer this description, and, interestingly enough, in 2 of them the injuries were old. The essential details of these 3 cases are included in table 1. In the first and

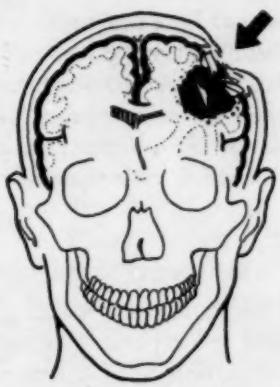

Fig. 1.—Traumatic intracerebral hemorrhage following direct injury, showing the mechanism of its production. The injury was a compound comminuted depressed fracture with laceration of the cerebral vessels by bone fragments.

TABLE 1.—*Intracerebral Hemorrhages Consequent to Laceration of the Brain*

Case No.	Age	Sex	How Injured	Period of Survival	Location of Lesions in Scalp	Injury to Brain	Size and Location of Hemorrhage
1	67	♂	Struck by automobile	61 hours	Left temporo-occipital region	Local depressed fracture of skull with laceration of brain	Recent extensive hemorrhage into left temporal lobe
2	56	♂	Fall from train	18 years	Left parietal region	Local depressed fracture of skull	Old large hemorrhagic cavity in left parietal region
3	57	♂	Gunshot wound	22 years	Left upper central region	Local compound comminuted fracture of skull	Old small hemorrhagic cavity in upper portion of left precentral gyrus

second cases the injury was due to a compound comminuted depressed fracture of the skull. In the second case the lesion was studied some eighteen years after the original injury. The characteristics of this lesion are shown in figure 2. In the third case the brain was examined twenty-two years after an accidental gunshot wound of the head. It presented an irregular cavity in the upper portion of the left precentral gyrus. The details of this lesion have been described in another connection.[2] The old, multilocular cavity was not very extensive, probably the result of indriven fragments of bone as well as of the passage of the bullet. Its fairly smooth walls presented evidence of pigmentation even after this long interval, indicating that a blood clot had occupied this space.

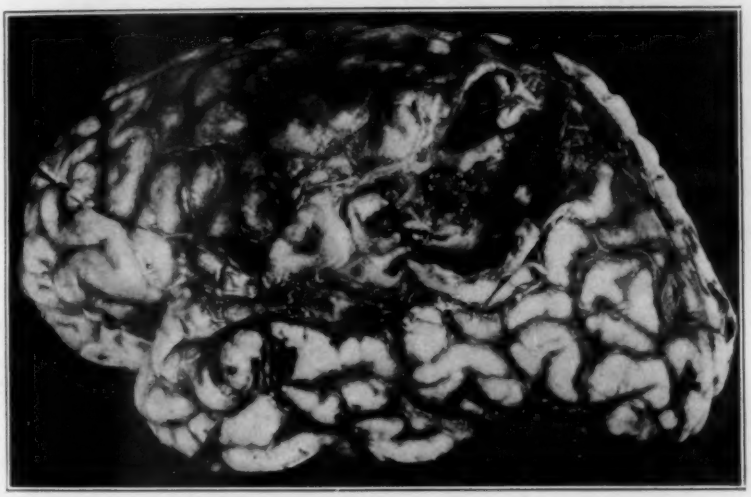

Fig. 2 (case 2).—Traumatic porencephaly. Note the old hemorrhagic cavity in the left parietal lobe consequent to compound comminuted depressed fracture of the cranial vault.

Traumatic Intracerebral Hemorrhage Due to Coup-Contrecoup Injury.—In this larger group of cases cerebral damage was sustained while the head was in motion in the course of an automobile accident or a fall. If the intracerebral hemorrhage in these cases is to be considered actually an effect of the *coup-contrecoup* mechanism, it is necessary that the lesion conform to the rules as far as its location is concerned, and it should be comparable in this regard to contusions, which are the most typical lesions in this group. A brief statement of the essential factors is here in order.

2. Courville, C. B., and Kimball, T. S.: Histologic Observations in a Case of an Old Gunshot Wound of the Brain, Arch. Path. **17**:10 (Jan.) 1934.

1. Injury to the frontal region produces a *coup* lesion of the frontal lobes, not infrequently accompanied by a *coup* or *contrecoup* lesion of one or both temporal lobes.

2. Injuries to the temporal and parietal regions commonly produce *contrecoup* lesions; less commonly, *coup* lesions of the temporal lobe.

3. Injuries to the occipital region produce *contrecoup* lesions of the basilar surfaces of the frontal lobes or of both the frontal and the temporal lobes. Occipital injuries do not produce *coup* lesions.

As will be shown, this group of intracerebral hemorrhages fill all the postulates for *coup-contrecoup* lesions, since they were sustained when the head was in motion and were located in parts of the brain which are ordinarily contused by such injuries.

ANATOMIC CLASSIFICATION

From the study of the cases in our series, we have been able to elaborate the following classification of traumatic intracerebral hemorrhage: (1) hemorrhage into the frontal lobes, which may be either *coup* or *contrecoup,* adjacent or central;[3] (2) hemorrhages into the temporal lobes, which may be *coup* or *contrecoup,* adjacent or central; (3) bilateral cerebral lesions, usually frontal or temporal, indicating both *coup* and *contrecoup* effects; (4) hemorrhage into the ganglionic region which may be either *coup* or *contrecoup* in effect, and (5) hemorrhage into the cerebellum, essentially a *coup* effect.

Because of the individual characteristics of the lesions in the various anatomic locations we have chosen to discuss them on this basis.

TRAUMATIC HEMORRHAGES INTO THE SUBSTANCE OF THE FRONTAL LOBES

Traumatic hemorrhage into the frontal lobes seems to be a fairly common consequence of injury and may be the result of either a *coup* or a *contrecoup* injury. In 13 of our 38 cases the hemorrhage proved to be located in this region. Reference to table 2 discloses some interesting

3. In this connection it is necessary to define the words "adjacent" and "central," which have been used in the foregoing classification. In this sense, "adjacent" refers to a major hemorrhage directly consequent to a focal contusion of the cortex and subcortex. It is not meant to include, however, the hemorrhage which is an essential part of the contusion itself. In some instances, when the bruise is severe and when some preexisting disease of the blood vessel favors its rupture, a gross effusion of blood into the lobe takes place, which complicates the original lesion and undoubtedly assists in bringing about the patient's death. On the other hand, "central hemorrhages" are those effusions which occur primarily in the centrum of the frontal or the temporal lobe, less commonly elsewhere and often with little or no evidence of focal contusions of the cortex. At times these central hemorrhages extend to and rupture through the cortex, so that this lesion might possibly be mistaken at operation for an "adjacent" hemorrhage.

TABLE 2.—*Hemorrhages Into the Frontal Lobes*

Case, Sex, Age	How Injured	Period of Survival	Location of Lesions in Scalp	Cerebral Contusions	Cerebral Hemorrhages	Conscious Interval
			A. Coup Hemorrhages			
			Adjacent			
4 ♂ 29	Automobile collision	22½ hours	Right and left frontal region	Right and left frontal and temporal lobes	Moderate-sized hemorrhages into right and left frontal lobes	0
5 ♂ 40	Automobile accident	40 hours	Right and left frontal region	Left frontal lobe	Small hemorrhage into left frontal lobe	0
			Central			
6 ♀ 43	Automobile collision	13½ days	Right frontal region	None	Very large hemorrhage into right frontal lobe	2 to 3 hours
7 ♂ 45	Struck by automobile	6¾ hours	Right and left frontal regions	Right and left frontal and right temporal lobes	Small hemorrhage into right and left frontal lobes	0
8 ♂ 72	Struck by automobile	6 days	Right and left frontal regions	Right frontal and temporal lobes	Very large hemorrhage into right frontal lobe	¾ hour
9 ♂ 78	Fall	28 hours	Right and left frontal regions	Right and left frontal lobes	Very large hemorrhage into left frontal lobe	Coma for 2 hours; conscious (?); coma
			B. Contrecoup Hemorrhages *			
			Medial Frontal Hemorrhage with Contusions (Typically Adjacent)			
10 ♂ Adult	Automobile accident	50 hours	Occipital	Right and left frontal lobes	Moderate adjacent hemorrhages into left and right frontal lobes	0
11 ♂ 48	Fall (epilepsy)	16½ hours	Right occipital	Right and left frontal lobes	Moderate adjacent left frontal hemorrhage	Complicated by convulsions
			Lateral Frontal Hemorrhage Without Contusion (Central with Rupture to Surface [?])			
12 ♂ 44	Fall	7½ days	Left parietal region	Right frontal and temporal lobes	Moderate adjacent hemorrhage into right frontal lobe	Coma few hours; conscious 5 days; coma 4 days
13 ♂ 62	Fall	4 days	Right occipital region	Right and left frontal lobes	Massive adjacent left frontal hemorrhage	0
14 ♂ 55	Struck by automobile	3½ days	Right occipital region	Right and left frontal, left temporal lobes	Moderate adjacent left frontal hemorrhage	Incomplete latent interval
15 ♂ 72	Automobile accident	9 days	Left occipital region	Right and left frontal lobes	Moderate adjacent right frontal hemorrhage	Incomplete latent interval
			Both Adjacent and Atypically Central Hemorrhage			
16 ♂ 58	Struck by automobile	7¾ days	Right and left occipital regions	Right and left frontal and right temporal lobes	Numerous moderate adjacent and central hemorrhages into both frontal lobes	Coma for hours; conscious 3 days; coma 4 days

* See discussion in text for classification of this group of cases

points. In the first place, it will be noticed that hemorrhage following either *coup* or *contrecoup* injury to the frontal region may be adjacent or central. However, as will be shown, these hemorrhages are not so simply classified anatomically. The typical adjacent hemorrhages with gross external contusions are usually found within the medial aspects of the frontal lobes. There is a second type of hemorrhage, which occurs in the frontal centrum and extends to the surface of the lobe through a

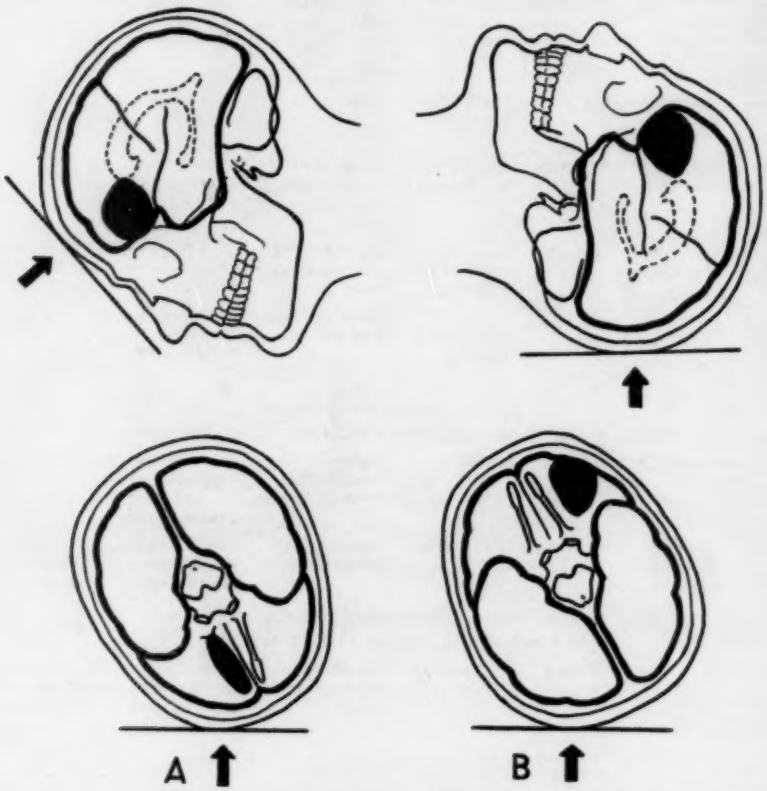

Fig. 3.—Traumatic hemorrhage into the frontal lobe, showing the mechanisms of its production. *A*, parasagittal hemorrhage from *coup* injury; *B*, lateral hemorrhage from *contrecoup* injury.

semilunar slit along the inferolateral margin of the lobe. Whether this is in fact an adjacent or a central hemorrhage will be discussed in the proper section. Typical *contrecoup* hemorrhages are rare, being found in only 1 case and then in association with typical bilateral adjacent hemorrhage.

Adjacent Frontal Hemorrhages.—Whether a *coup* or a *contrecoup* effect, according to our definition an adjacent hemorrhage is part of a

focal traumatic lesion of the basilar surface of the frontal lobe. The contusion usually involves the medial aspect of the basilar surface, ordinarily just lateral to the anterior portion of the straight gyrus. From the external contused area, often limited in extent, there extends upward and outward into the brain a narrow hemorrhagic cavity, the anteroposterior extent of which varied considerably in the cases studied. In cases of mild injury it may be a slitlike space in which hemorrhage is seen at autopsy. In other cases this cavity may extend throughout the length of the frontal lobe, rupturing into the anterior horn of the corresponding lateral ventricle with consequent ventricular hemorrhage. In fact, this mechanism constitutes one of the numerous forms of traumatic intra-

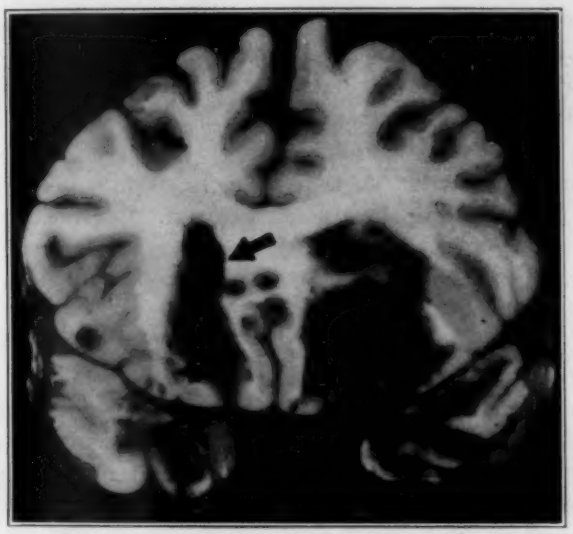

Fig. 4 (case 11).—Bilateral traumatic "adjacent" frontal hemorrhages with rupture into the anterior horn of the lateral ventricle (arrow).

ventricular hemorrhage. A fairly characteristic lesion of this sort is shown in figure 2.

Lateral Frontal Hemorrhage, Possibly Central.—The second type of intrafrontal hemorrhage, which closely resembles the central type in some respects, is one in which the clot is found more laterally in the lobe. This lesion seems to occur with injuries definitely to one side or the other of the occiput. The hemorrhage is often fairly large and may excavate a considerable cavity in the substance of the homolateral frontal lobe. It extends almost invariably to the surface of the lobe by a slit along the curved inferolateral margin of the frontal lobe. A typical lesion of this variety is shown in figure 3. It may rupture into the anterior horn of the corresponding ventricle. The prolonged period of

survival with the suggestion of a lucid interval clinically and the absence of associated cortical contusion indicate that this lesion is a variety of true central hemorrhage.

Typical Central Hemorrhages of the Frontal Lobe.—Only four typical central hemorrhages occurred as a result of a *coup* injury, and in 3 cases the effusion was large (fig. 4). In 1 case of *contrecoup* injury several paracentral hemorrhages were observed in association with adjacent hemorrhages. Central hemorrhages in *coup* lesions are frequently accompanied by a more or less definite contusion of the subfrontal region and are therefore indicative of a rather severe injury to the head.

In spite of this, it is of interest to note that there is a rather long period of survival, suggesting a progressive lesion in such cases. Attention should be called to 1 case in particular (case 6, table 2). A patient survived for thirteen and one-fourth days after an injury to the head in which the essential lesion was a massive hemorrhage into the right frontal lobe. Since there was a period of consciousness following the accident, it seems quite likely that the hemorrhage, evidently initiated in some way by the injury, continued until death ensued. In this sense the lesion is characteristic of a delayed traumatic hemorrhage. More attention will be drawn later to this question of delay in onset of the symptoms provoked by the hemorrhage.

As for the *contrecoup* type of hemorrhage, although it is adjacent in every case, the rather prolonged period of survival is a matter of special interest. The patient survived a number of days in all but 2 cases. It should also be noticed that in this group of cases there occurred in a number of instances what appeared to be an interval of consciousness after transitory short periods of coma, with a subsequent relapse into coma and eventual death.

TRAUMATIC HEMORRHAGES INTO THE TEMPORAL LOBE

From a study of table 3 it will be found that *coup* hemorrhages of the temporal lobe, either adjacent or central, were rather rare. This is in accord with the relative infrequency of contusions of the temporal lobe on the same side as the injury. *Contrecoup* lesions of the temporal lobe are the rule. It will furthermore be observed that in the larger group of *contrecoup* hemorrhages, most effusions occur in the centrum of the lobe. They are not accompanied with local contusions, although at times *coup* contusions of the frontal lobe may be present. This leads one to conclude that, although temporal contusions may be so severe as to provoke a local hemorrhage, central hemorrhages are more apt to occur as a *contrecoup* effect of the injury. Furthermore, these central effusions into the central lobe are frequently large and in this regard would correspond closely to spontaneous hemorrhages into the brain.

TABLE 3.—*Hemorrhages Into the Temporal Lobe*

Case, Sex, Age	How Injured	Period of Survival	Location of Lesions in Scalp	Cerebral Contusions	Cerebral Hemorrhages	Conscious Interval
			A. Coup Hemorrhages			
			Central			
17 ♂ 23	Motorcycle accident	3½ days	Right frontal and temporal region	None	Small central hemorrhage into right temporal lobe	0
18 ♀ 50	Automobile accident	17½ hours	Left temporal region	Left and right frontal and right temporal lobes	Large central hemorrhage into left temporal lobe	0
			B. Contrecoup Hemorrhages			
			Adjacent			
19 ♂ 35	Fall	15 hours	Left temporal region	Right and left temporal lobes	Large adjacent hemorrhage into right temporal lobe	0
20 ♂ 38	Fall from horse	61 hours	Left temporoparietal region	Right temporal lobes	Massive adjacent hemorrhage into right temporal lobe with consequent subdural hemorrhage	No preliminary coma; coma after 18 hours
21 ♂ 49	Struck by automobile	18 hours	Left frontal region	Right temporooccipital region	Moderate adjacent hemorrhage into right temporooccipital region	0
			Central			
22 ♂ 57	Fall	10 days	Right temporal region	None	Massive central hemorrhage into left temporal lobe	8-9 day interval
23 ♂ 79	Struck by automobile	3 days	Right frontal region	None	Multiple small central hemorrhages into left temporal lobe	Suggestive interval
24 ♂ 78	Struck by automobile	32 hours	Right frontotemporal region	None	Massive central hemorrhage into left temporal lobe	0
25 ♂ 35	Fall	4½ days	Right temporal region	None	Massive central hemorrhage into left temporal lobe	No interval; survival period prolonged by operation
26 ♂ 75	Struck by motorcycle	8½ days	Right frontotemporal region	Right frontal and temporal lobes	Massive central hemorrhages into left temporal lobe	Preliminary coma, then partial recovery followed by coma
27 ♂ 27	Fall	4 days	Right temporal region	None	Massive central hemorrhage into left temporal lobe	Interval 1½ hours
28 ♂ 48	Fall	About 6 days	Right frontal region	Left temporal lobe	Massive hemorrhage into left temporal lobe	Interval ?
29 ♂ 48	Automobile accident	7 months	?	None	Old hemorrhagic cavity with extension to basilar surface of temporal lobe and lateral ventricle	?

Particular emphasis should be placed on this point, because it is this group of cases in which the hemorrhage is severe enough to require serious clinical consideration, demanding therapeutic attention in and of itself. This differs from adjacent intracerebral hemorrhage, which is a part of an already serious and extensive lesion. Moreover, the patients frequently have a prolonged period of survival, at times with a lucid interval, or symptoms may come on gradually and progressively after a relatively minor frontal injury. This also suggests the likelihood that such hemorrhages are progressive lesions, initiated in some way by the injury and producing symptoms by a gradual accumulation of blood in the centrum. A deepening coma ultimately results in the patient's death.

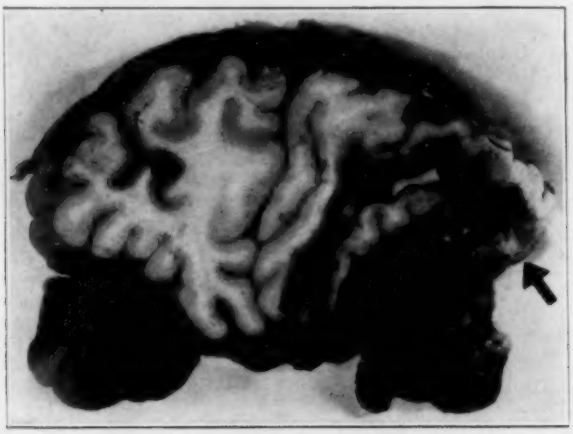

Fig. 5 (case 13).—"Central" traumatic frontal hemorrhage with rupture to the surface (arrow) along the inferolateral margin of the lobe.

Adjacent Hemorrhages into the Temporal Lobe.—Adjacent hemorrhages of the temporal lobe correspond to those of the frontal lobe and evidently have a similar mechanism. A severe temporal contusion is accompanied by a laceration of the cortex and subcortex. This laceration extends into the brain, tearing some of the regional vessels, with consequent hemorrhage. When the effusion is of sufficient size, a cavity is excavated in the white matter of the temporal lobe, at times followed by rupture into the interior horn of the lateral ventricle, another cause of traumatic intraventricular hemorrhage. Usually this hemorrhage is small, but if a large vessel is lacerated or some preexisting vascular disease predisposed to a more extensive effusion the entire central portion of the lobe may be excavated (fig. 5). Such hemorrhage adds to the edema provoked by the original contusion and no doubt contributes much to the fatal issue in these cases. These hemorrhages likewise

give rise to definite lateralizing phenomena, which encourage the surgeon to do a decompression in the hope of finding a subdural clot. At operation the clot may rupture spontaneously through the exposed cortex into the field of the decompression, or it may be discovered by needling the temporal lobe. Indeed, with a basilar contusion it may be difficult for the surgeon to determine whether he is dealing with a primary central hemorrhage or an adjacent one.

Central Hemorrhages of the Temporal Lobe.—As will be seen by referring to table 3, gross hemorrhages into the temporal or temporo-occipital region may be either a *coup* or a *contrecoup* effect, usually the latter. The resulting lesion seems to be characteristic in that there is

Fig. 6 (case 8).—Unusual type of "central" traumatic hemorrhage into the frontal lobe with rupture into the body of the right lateral ventricle (arrow). A small "adjacent" hemorrhage into the ipsilateral temporal lobe is also shown.

a massive effusion of blood into the temporal or temporo-occipital centrum without local cortical contusions. This is an area rarely involved by spontaneous hemorrhage. These hemorrhages are often extensive (fig. 6), although in 2 cases in our series the hemorrhages were small.

Although they are obviously *contrecoup* lesions, central hemorrhages into the temporal lobe are relatively infrequent. This may be explained by some by the fact that hemorrhage does not occur unless the injury is severe. On the other hand, the absence of superficial contusion in such cases seems to make this supposition rather untenable. Arteriosclerosis may play an important role, for a considerable number of the patients are beyond middle life. On the other hand, in several instances in this study the patient was relatively young (23 years of

age in 1 case). The influence of other vascular diseases, such as syphilis, seems to be negligible, although the possibility of hypoplasia of the arteries, which predisposes to easy rupture by trauma, may account for this particular phenomenon. These facts make it seem very likely that either some peculiar mechanism of the injury itself or, more probably, some other predisposing factor accounts for its occurrence.

These effusions excavate an elongated fusiform cavity in the temporal and adjacent occipital centrum, conforming to some extent to the radiation of white fibers in these lobes. The occurrence of a lucid interval after a preliminary period of unconsciousness suggests that the hemorrhage is a progressive one, increasing in size as the hours and days pass. The longest period of survival in this series was ten days. In this respect the lesion qualifies as delayed traumatic apoplexy. The

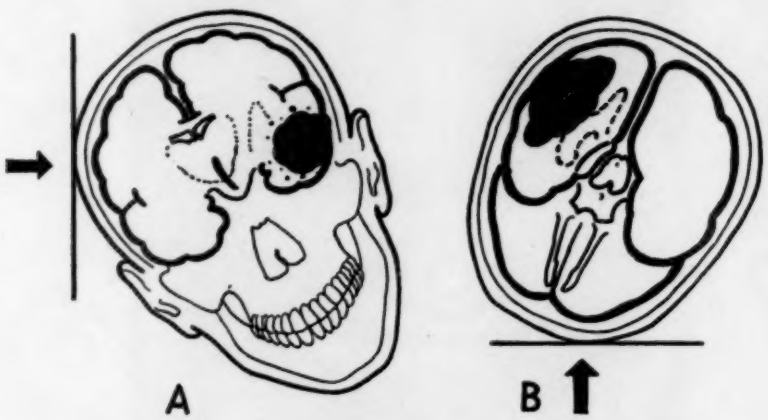

Fig. 7.—Traumatic hemorrhage into the temporal lobe, showing the mechanism of its production. *A, contrecoup* "adjacent" hemorrhage, a part of a gross contusion of the lobe; *B, contrecoup* "central" hemorrhage.

mechanism of progressive bleeding scarcely accounts for those cases in which weeks or even months elapse between the time of injury of the vessel and death. The evolutionary character of the lesion is strongly indicated by the progressive clinical course when the patient survives for several days.

It is a fairly common thing for these large effusions to rupture through the cortex or into a ventricle. There seems to be no particularly specific location where this rupture takes place. At times it occurs well forward in the temporal lobe, often through the superior temporal gyrus or sulcus. More commonly, however, it occurs lower on the dorsolateral surface, through the middle or inferior gyri or sulci, well toward the posterior portion of the lobe. Not infrequently, however, the effusion ruptures through the basilar surface of the lobe. The overlying leptomeninges are torn, and there is a gross effusion of blood into the subdural

space. In such cases the findings at operation may lead to the belief that the subdural hemorrhage is primary, the surgeon not being able to discover its exact source. Not infrequently the effusion breaks through into the lateral ventricle (fig. 7). In the great majority of cases a massive hemorrhage into the temporal lobe results fatally unless by chance the cavity is surgically excavated either directly through the cortex or by draining the effusion in the subdural space after its rupture. Evacuation of the subdural clot, however, is often incomplete and ineffectual, and death occurs.

HEMORRHAGES INTO BOTH FRONTAL AND TEMPORAL LOBES

As will be noted in table 4, hemorrhages into both the frontal and the temporal lobes are relatively infrequent. In certain severe injuries

TABLE 4.—*Hemorrhages Into the Frontal and Temporal Lobes*

Case No.	Age	Sex	How Injured	Period of Survival	Location of Lesions in Scalp	Injury to Brain	Size and Location of Hemorrhage
				A. Coup Hemorrhage			
30	35	♂	Struck by automobile	12 hours	Right and left frontal region	Right and left frontal and temporal lobes	Adjacent hemorrhages in right frontal and temporal and left frontal lobes
				B. Contrecoup Hemorrhage			
31	79	♂	Fall	42 hours	Right occipital region	Left frontal lobe	Adjacent hemorrhage in left frontal and central hemorrhage in left temporal lobe

both the temporal and the frontal lobes are injured, and (rarely) hemorrhages into the contusions in both these locations may contain gross blood clots with extension into the centrum. This is probably a matter of coincidence in severely injured patients and has no clinical significance. It will be noted that in most of the cases the hemorrhages were "adjacent" except in the second case, in which the lesion was "central."

BILATERAL HEMORRHAGES INDICATING BOTH COUP AND CONTRECOUP EFFECTS

In table 5 the essential findings in a series of 4 cases are recorded in which hemorrhages were observed in both cerebral hemispheres, occurring as a rule in a line which points out the line of force produced by trauma. This through and through effect is manifested by hemorrhages extending through the centrum of the brain. An exception is noted in case 33, in which there were observed hemorrhages secondary to contusions of both temporal lobes, a rather unusual situation. These

effusions were small, the largest apparently located on the side of a trauma. A rather interesting situation is found in the first case in this series, in which hemorrhages were observed in both external capsules and the left lenticular nucleus. In the following section further attention will be drawn to the question of hemorrhages in the ganglionic region.

This series of cases is probably of no special clinical significance, those patients who survived for a few hours having been so seriously hurt that the intracerebral hemorrhages were simply a part of the general pathologic picture. Perhaps of greater importance in these cases is the suggestion of the true *coup-contrecoup* mechanism. Attention has already

TABLE 5.—*Bilateral Hemorrhages Indicating Both Coup and Contrecoup Effect*

Case, Sex, Age	How Injured	Period of Survival	Location of Lesion in Scalp	Injury to Brain	Size and Location of Hemorrhage	Conscious Interval
32 ♂ 70	Automobile accident	3 hours	Left temporal region	Right temporal lobe	Multiple small to moderate central hemorrhages in left and right external capsules and left lenticular nucleus	0
33 ♀ 50	Struck by automobile	5½ days	Left temporo-occipital region	None	Multiple small to moderate central hemorrhages into right temporal and left temporo-occipital regions	0
34 ♀ 66	Automobile collision	18½ hours	Left temporal region	Right and left temporal lobes	Moderate left and small right adjacent hemorrhages in temporal lobes	0
35 ♂ 20	Fall	29½ hours	Right occipital region	Left frontal and temporal lobes	Multiple moderate and central hemorrhages into left frontal and temporal lobes and small hemorrhage into right temporo-occipital centrum	0

been drawn by one of us (Courville) to certain cases in which a line of lesions through the brain is seen at autopsy. This suggests that the line of force extends directly through the brain across the diameter of the skull, indicating that the *contrecoup* lesion is probably a result of direct transmission of force rather than of any of the peculiar mechanisms which have been suggested. The string of lesions in this series of cases strongly indicates that this is the case. Why this occurs in a relatively few cases and why the ganglionic region is apt to be spared it is difficult to determine. The central, or ganglionic, part of the brain, lying as it does beneath the inferior margin of the falx, may be more easily displaced from side to side without causing serious injury in this location.

HEMORRHAGES IN THE GANGLIONIC REGION

In table 6 is recorded a series of cases in which small hemorrhages were observed in the lenticular nucleus, commonly the putamen, or extending into the *external* capsule. In half of these cases the hemorrhages were also seen in other locations and have already been included in other groups. In the remaining 3 cases the hemorrhages were limited

TABLE 6.—*Traumatic Hemorrhages Into the Ganglionic Region (External Capsule and Lenticular Nucleus)*

Case, Sex, Age	How Injured	Period of Survival	Location of Lesion of Scalp	Injury to Brain	Size and Location of Hemorrhage	Conscious Interval
7* ♂ 58	Struck by automobile	7¾ days	Occipital region	Right and left frontal and right temporal lobes	Multiple moderate adjacent and central right and left frontal hemorrhages; clot about size of marble in right lenticular nucleus	Coma few hours, then conscious three days; terminal coma four days
36 ♂ 62	Struck by automobile	7 days	Left temporal region	None	Small hemorrhages left lenticular nucleus; large hemorrhage right external capsule	Persistent coma
37 ♂ 62	Automobile collision	3¼ days	Left temporal region	Right temporal lobe	Small hemorrhage into right external capsule	0
38 ♀ 6	Fall	4½ hours	Right frontotemporal region	None	Moderate hemorrhage into left external capsule	0
2* ♂ 40	Automobile accident	40 hours	Right and left frontal regions	Left frontal lobe	Small adjacent hemorrhage in left frontal lobe; marble-sized clot in left lenticular nucleus	0
27* ♂ 70	Automobile accident	8 hours	Left temporal region	Right temporal lobe	Multiple small to moderate hemorrhages in left and right external capsules and left lenticular nucleus	0
34 ♂ 18	Automobile accident	2½ hours	Right and left frontal regions	Right and left frontal and temporal lobes	Marble-sized clot into right lenticular nucleus	0

* It will be noted that there is some duplication in this table, some of the cases being found also in previous groups.

to the external capsule or the lenticular nucleus (fig. 8). These hemorrhages too may be manifestations of either *coup* or *contrecoup* injury; that is, they may occur on the same side as the external injury or on the opposite side. Of particular interest in this group are those cases in which an injury to the frontal or the occipital region results in a small focal hemorrhage in the lenticular nucleus of the same or the opposite side. Such an injury is probably a modification of the "through and through type" of trauma, as is suggested by some of the cases in the group. Since the occipital lobe is unaffected by either *coup* or

contrecoup lesions, the absence of hemorrhages in this lobe tends to impair the otherwise complete impression of through and through injury in these cases. Attention will be again drawn in a later section to this matter of hemorrhages in the ganglionic region.

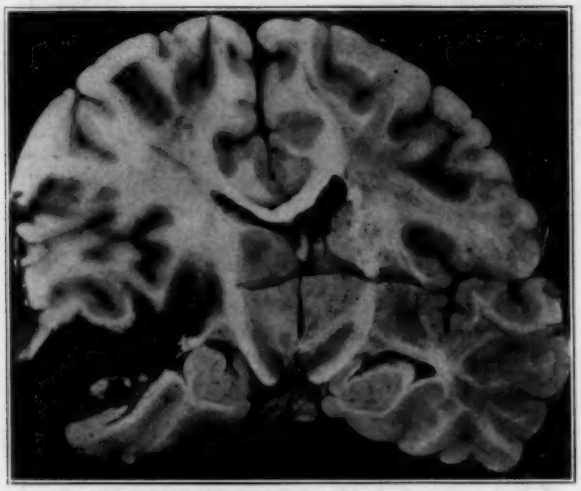

Fig. 8 (case 20).—"Adjacent" traumatic hemorrhage into the temporal lobe. The consequent edema and distortion of the ventricular pattern are also shown.

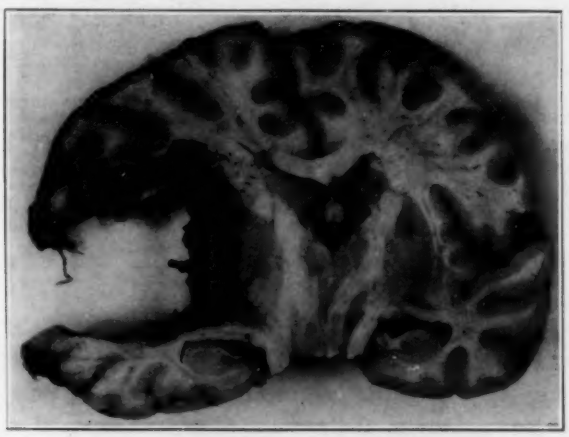

Fig. 9 (case 25).—"Central" traumatic hemorrhage into the temporal lobe. The unusual size of the cavity and the place of rupture to the surface as well as consequent edema and distortion of the ventricular pattern are shown.

COMMENT

It will be seen from a study of this series of cases that intracerebral hemorrhages are essentially a *coup-contrecoup* effect, the injury being

Fig. 10 (case 26).—Massive "central" traumatic hemorrhage *contrecoup* into the temporal lobe with rupture into the lateral ventricle as well as to the surface (arrows). A *coup* hemorrhage of the frontal lobe is also shown. The broken line shows the direction of force.

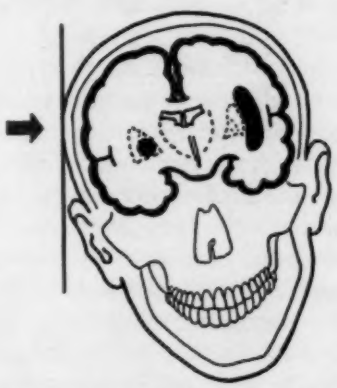

Fig. 11.—Traumatic hemorrhage into the ganglionic region, showing the mechanism of production. The *coup* hemorrhage occurred into the lenticular nucleus and the *contrecoup* hemorrhage into the external capsule.

sustained with the head in motion. An exception to this rule is the relatively rare occurrence of hemorrhage into the brain following compound comminuted depressed fractures with laceration of the brain by indriven fragments of bone or foreign bodies or probably still more rare instances of penetrating wounds of the skull by a bullet or an edged weapon.

The large group of *coup-contrecoup* hemorrhages may be divided into two subgroups—*adjacent* or *secondary* ones, which are a part of a severe contusion, and *central,* or *primary,* ones in which hemorrhages occur primarily in the centrum of the lobe. Adjacent hemorrhages are to be grouped with the contusion of which they are an essential part, and the severity of the hemorrhage in these cases is dependent largely on the force of the original injury and the friability of the vessels in a given

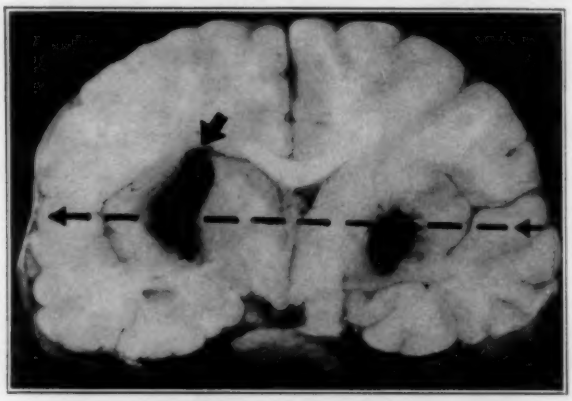

Fig. 12 (case 32).—Traumatic hemorrhages into the right external capsule and the left lenticular nucleus. The hemorrhage on the right has broken into the lateral ventricle (arrow). The line of force is indicated by the interrupted line.

brain. From the standpoint of traumatic apoplexy, no further attention need be given this group of adjacent or secondary hemorrhages.

Of the group of central, or primary post-traumatic, cerebral hemorrhages there is more to be said. It has been definitely shown that this group of hemorrhages, like the adjacent ones, are a manifestation of the *coup-contrecoup* mechanism, particularly *contrecoup.* At times these hemorrhages are small. On other occasions they are sufficiently extensive to assume clinical importance. This is particularly true of those which occur in the frontal or the temporo-occipital region and which at times seem to follow a relatively minor injury. In these instances, after a latent interval, a progressively increased intracranial pressure results in coma. In this respect, a large central hemorrhage produces a clinical picture which resembles more or less closely that of dural hemorrhage

with a lucid interval, with which it may be easily confused clinically. This interval was prolonged in 1 of our cases as long as eight to nine days, death occurring on the tenth day after the original minor injury.

There is probably some factor other than the *contrecoup* mechanism in these cases. Otherwise it would be relatively much more common, comparable perhaps in frequency to the cortical contusion, which is found in approximately two thirds of patients coming to autopsy after injury of the head. One possible reason for this is that the lesion is a deeper one and that therefore the part affected is less apt to be traumatized as a result of the force of the blow. The force transmitted through the brain is more widely diffused in these distant parts, which is not so easily possible in the closely invested frontal fossae.

Since a number of these hemorrhages occurred in patients beyond middle age, the possibility of arteriosclerosis or other vascular disease must also be considered. It is logical to believe that atherosclerosis may predispose to rupture of a vessel which would otherwise be unaffected in a younger patient. On the other hand, it must be admitted that a fair number of hemorrhages have occurred in young adult patients in whom no arteriosclerosis was present. Whether or not hypoplasia of the cerebral arteries, which is observed in some instances is a cause of hemorrhage cannot now be determined with certainty. One of us (Courville) has observed that hypoplasia of the cerebral vessels does play an important part in some cases in which gross effusions of blood on the basis of relatively minor injuries have taken place. On the other hand, whether this phenomenon can be invoked to account for all central hemorrhages in younger persons is only a matter of conjecture. Further study must be given this point before a final answer can be made.

"DELAYED TRAUMATIC APOPLEXY"

Much has been said in the literature about "delayed traumatic apoplexy," a term now almost half a century old. The designation carries with it the idea of gross hemorrhage into the brain occurring some time after an injury to the head. The question has important connotations from a medicolegal standpoint and is therefore an important one to settle one way or the other. Since, in this study, the basis has been laid for an understanding of the mechanism and morbid anatomy of traumatic intracerebral hemorrhage, it seems advisable to take the next step and determine, if possible, whether traumatic hemorrhage into the brain can be delayed and how long, what its predisposing lesions may be and how this supposed entity differs, if it does differ, from hemorrhage as a consequence of arteriosclerosis with or without hypertension.

The history of this interesting question of delayed post-traumatic apoplexy has been divided by Duret [4] into four periods, which bring the investigator up to the time of publication of Duret's monograph on craniocerebral injuries in 1922. The first period begins with the introduction of the concept by Bollinger [5] in 1891, who reported a series of 4 cases in which the patients died suddenly with an apoplectic hemorrhage after a period of lucidity varying from twelve to fifty days after injury to the head. In 3 of these cases a blood clot was found in the fourth ventricle, and in the fourth a hematoma was found in the white substance of the centrum ovale, adjacent to the lateral ventricle. Bollinger expressed the belief that these hemorrhages occurred in an area of softening provoked by the cranial shock. In the next six or seven years a number of cases were reported which seemed to confirm this opinion. In 1 in particular, the case reported by Michel,[6] the patient died eight days after injury. At autopsy a hemorrhage about the size of an egg was found in the right occipital lobe, which had ruptured into the occipital horn of the ventricle. This hemorrhage was evidently the result of a *contrecoup* lesion, the patient having sustained an injury to the frontal region.

During the second period, certain objections to the theory were raised by some observers, who questioned whether such hemorrhages are truly traumatic. Langerhans,[7] in particular, expressed the opinion that the hemorrhage is incident to some predisposed vascular condition, such as hypoplasia, anemia or arteriosclerosis, the diseased vessel being ruptured by the shock of trauma.

In 1904 Bailey [8] recognized three varieties of traumatic hemorrhage. He stated that the first type occurs at the moment of injury, the rupture of the vessel being due to the immediate force of the injury or to the increased arterial hypertension provoked by it. In the second type, vascular rupture is produced a little time after the injury, the exact mechanism of which was not possible to determine. In the third type, apoplectiform symptoms appeared a considerable time after injury, apparently due to thrombosis in the region of the brain traumatized by the accident.

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4. Duret, H.: Traumatismes cranio-cérébraux: Accidents primitifs, leurs grandes syndromes, Paris, Félix Alcan, 1922, vol. 3, pt. 2, pp. 833-851.

5. Bollinger, O.: Ueber traumatische Spätapoplexie; ein Beitrag zur Lehre von der Hirnerschütterung, in Internationale Beiträge zur wissenschaftlichen Medizin, Festschrift, Rudolf Virchow gewidmet zur Vollendung seines 70. Lebenjahres, Berlin, A. Hirschwald, 1891, vol. 2, pp. 457-470.

6. Michel, E.: Ein Beitrag zur Frage von der sogenannten traumatischen Spätapoplexie, Wien. klin. Wchnschr. **9**:789-793, 1896.

7. Langerhans, R.: Die traumatische Spätapoplexie, Berlin, A. Hirschwald, 1903.

8. Bailey, P.: Traumatic Apoplexy, M. Rec. **66**:528, 1904.

During this period Lafforgue [9] introduced the conception that delayed cerebral hemorrhage is due to an earlier hemorrhage, or in other words, a hemorrhage occurring in two stages.

In 1905 Lambert [10] concluded that in certain cases of traumatic hemorrhage occurring either early or late, the arteries have been structurally altered by preexisting disease constituting a *locus minoris resistentiae*. The diseases which, according to him, predispose to rupture of the vessels are alcoholism, gout, arteriosclerosis and syphilis.

In the third period, investigators were concerned largely with the discussion of certain types of hemorrhages, particularly those in the pontobulbar region or in the meninges which occurred at varying intervals after injury to the head. These lesions consisted of local collections of old blood in the pons or in the subarachnoid space which gave rise to symptoms several weeks or even months after the injury.

In the fourth period, primary traumatic intracerebral hemorrhages, little or large, were recognized as being possible after injury, and some extended the conception to include intraventricular and pontobulbar hemorrhages. The microscopic investigations of von Hölder [11] led him to conclude that delayed hemorrhages are the result of multiple small lesions affecting the walls of the blood vessels, consisting of small tears and consequent dilatations of local capillaries; in other words, that they are small aneurysms with focal hemorrhages within the perivascular sheath or in its immediate vicinity. Hanzer [12] subsequently described the existence of small areas of softening in the nervous centers along the tract of the axis of percussion. It was then concluded that these small microscopic lesions which followed injury, although silent for some time, ultimately permitted a gross hemorrhagic effusion in this vicinity through a rupture in the wall of the vessel.

To bring the subject up to date it must be said that, although certain basic truths have become evident in the passing years, there is still much confusion and uncertainty about the whole question. In 1926, Beitzke [13] drew certain conclusions which are in full accord with our observations. He stated (1) that traumatic intracerebral hemorrhage is always at the periphery of the brain and either directly beneath the point of injury or on the opposite side (*coup-contrecoup*) and (2) that if the hemorrhage

9. Lafforgue, E.: Hémorragies intra-craniennes traumatiques évoluant en deux temps, Bull. méd., Paris **18**:875-878, 1904.

10. Lambert, P.: Hémorragies cérébrales tardives d'origine traumatique; traumatische Spätapoplexie, Thesis, Paris, no. 411, 1906.

11. von Hölder, H.: Pathologische Anatomie der Gehirnerschütterung beim Menschen, Stuttgart, J. Weise, 1904.

12. Hanzer, cited by Duret.[4]

13. Beitzke, H.: Pathologisch-anatomisch Diagnostik an der Leiche nebst Anleitung zum Sezieren, Munich, J. F. Bergmann, 1926.

has taken place only after weeks there is the greatest doubt whether it is actually due to the injury. Kaufmann [14] emphasized the point that it is rare to find a traumatic hemorrhage in the basal ganglions, where spontaneous hemorrhages are so frequent.

In 1928, Naffziger and Jones [15] reported 3 cases of "late traumatic apoplexy." In 2 of the 3 the mechanism of injury was force applied directly to the head, the hemorrhages being in the temporal lobe beneath the point of injury. Since in our series the hemorrhage was sustained when the head was in motion, it is difficult to account for these lesions unless perchance some preexisting vascular lesion predisposed to rupture by local injury.

Undoubtedly cases will arise in which the mechanism is not clear. A case in point is that reported by Rosenhagen,[16] in which a right precentral subcortical hemorrhage was found about five weeks after a direct injury to the right frontoparietal region. Unfortunately, in many of these uncertain cases, other possible causes of hemorrhage are not sought and eliminated.

The most conclusive recent article seems to be that of Eck.[17] He cited Singer,[18] who laid down certain postulates or criteria by which cases of presumed traumatic hemorrhages are to be judged. These postulates are as follows: 1. The injury to the head must be severe enough to cause definite injury to the intracranial content. 2. The vascular system must be sound before the injury. 3. Evidences of commotio cerebri and its consequences must lead directly to the apoplectic stroke. 4. Clinical objective signs of changes in the brain must be perfectly evident. 5. The interval between the development of the hemorrhage and the injury should not be less than one day or greater than eight weeks. Eck reported a case in which the condition seemed to answer to the description of a true post-traumatic intracerebral hemorrhage. The case reported by Bettinger [19] likewise seems to be a classic example.

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14. Kaufmann, E.: Pathology for Students and Practitioners, translated by S. P. Reiman, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 3, p. 1890.

15. Naffziger, H. C., and Jones, O. W., Jr.: Late Traumatic Apoplexy: Report of Three Cases with Operative Recovery, California & West. Med. **29**:361-364, 1928.

16. Rosenhagen, H.: Ueber postkommotionelle Veränderungen im Gehirn, zugleich ein Beitrag zur Frage der posttraumatischen Hirnblutungen, Klin. Wchnschr. **9**:601-604, 1930.

17. Eck, H.: Beitrag zur Lehre der traumatischen Spätapoplexie, Virchows Arch. f. path. Anat. **284**:67-83, 1932.

18. Singer, K.: Die sogenannte traumatische Spätapoplexie, Ztschr. f. d. ges. Neurol. u. Psychiat. **75**:127-137, 1922.

19. Bettinger, H.: Ueber traumatische Hirnblutung, Ztschr. f. d. ges. Neurol. u. Psychiat. **148**:570-573, 1933.

In summarizing the period since the appearance of Duret's discussion of the question, it seems evident that in many of the reported cases of delayed traumatic apoplexy the diagnosis was based on clinical evidence alone and is not to be relied on; in others, the hemorrhages were obviously spontaneous effusions into the basal ganglions, the previous trauma being merely incidental, and in still others trauma was probably contributory, with some underlying vascular disease or anomaly at fault. In many instances no serious attempt was made to eliminate other factors, and the case was reported as "delayed traumatic apoplexy."

In conclusion, a study of the literature indicates that these alleged delayed post-traumatic hemorrhages occur not only in the centrum but in or about the ventricles and in the pons as well. The three theories which have been utilized to account for the phenomenon are (1) the theory of necrotic softening, (2) the theory of preexisting alterations in the blood vessel wall and (3) the theory of recurrent hemorrhage. As for the first theory, it is believed that trauma results in the formation of multiple foci of softening in the brain, particularly in the immediate vicinity of the ventricular walls and in certain regions of the white matter, these foci resembling contusions of the cortex and subcortex. In the second theory it is predicated that the injury directly or indirectly produces changes in the wall of the blood vessels in the form of focal aneurysms, which were in turn predisposed to by arteriosclerosis, syphilis, alcoholism or Bright's disease. Secondary alterations are presumed to be due to a transitory physiologic or accidental arterial hypertension which traumatism exaggerated or favored by congestion of the centers of the brain. The third theory of delayed hemorrhage postulates a small primary hemorrhage in the region of the blood vessel as the direct result of the injury. As these initial lesions clear away, there remains a small residual aneurysm, a focal area of softening or regions of capillary apoplexy which permit the subsequent development of gross effusion of blood into the brain.

Just how well all this discussion of delayed traumatic apoplexy fits the basic principles brought out by a study of unequivocal post-traumatic cerebral hemorrhages remains to be told.

RELATION OF RECENT TO DELAYED POST-TRAUMATIC HEMORRHAGES

From our study of well defined and unmistakable hemorrhages into the cerebral centrum following injury, certain deductions may be drawn which should be useful in evaluating the problem of delayed post-traumatic hemorrhage.

As a result of our investigation it seems quite clear that symptoms of a hemorrhage may occur within a certain interval after trauma. Aside

from those due to direct laceration of the brain, these hemorrhages are essentially *coup-contrecoup* lesions. Although it is not definitely proved, it seems very likely that injuries resulting from a direct blow to the head at rest will not cause a hemorrhage within the brain substance unless there is some serious disease of the blood vessels. Furthermore, it seems obvious that the delayed post-traumatic hemorrhages in some of the reported cases bear some relation in time of occurrence and location to those which have been shown to be of traumatic origin. Such hemorrhages are to be expected in the centrum of the frontal or temporo-occipital region rather than in the posterior limb of the internal capsule, in the ventricles or in the brain stem as some have supposed. One of us (Courville) has observed that traumatic ventricular hemorrhages have usually proved to be secondary to extensive and massive hemorrhages within the centrum and are not primary in the sense of having their origin in paraventricular lesions.

The one question which has not been entirely established by our studies is that of the interval between the injury and the onset of clinical symptoms. In all of our cases in which the patients did not die within a day or two because of the severity of the injury the earliest symptoms came on within two or three days, although it must be admitted that a longer interval is possible. The difficulty lies in the fact that such hemorrhages are initiated by the trauma and develop progressively, differing in this respect from the apoplectiform onset of a spontaneous hemorrhage consequent to arteriosclerosis and hypertension. We are of the opinion that symptoms are likely to become manifest within a week or ten days at the latest and that the longer this interval the less likely it is that the hemorrhage is of traumatic origin.[20]

Although true traumatic hemorrhages do occur in elderly persons and arteriosclerosis *per se* does not seem to be a predisposing factor, an apoplectiform onset of symptoms with gross hemorrhage into the region of the basal ganglions in a person with arteriosclerosis and hypertension is to be considered as spontaneous even though the patient may have sustained an incidental injury some time before. One must also not be misled by minor injuries to the head in falls as a consequence of the "stroke." Moreover, this and other studies have shown that the interval capsule is less apt to be injured by blunt trauma than any other part of the brain. Although, to be sure, the lenticular nucleus has rarely been the seat of a traumatic hemorrhage, the lesion is small and is insufficient to bring about the patient's death. These facts should assist materially in distinguishing between traumatic and spontaneous hemorrhage.

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20. These intervals of survival are for fatal cases. No doubt such intervals may be longer in nonfatal cases. Our study furnishes no clue as to how long this interval may be.

Even in the presence of advanced arteriosclerosis, severe injury to the head has usually resulted in marked contusion of the brain rather than in intracerebral hemorrhage. No hemorrhages into the internal capsule have been observed. In cases of arteriosclerosis observed by us in which secondary and primary intracerebral hemorrhage had occurred, no instance of gross hemorrhage into the internal capsule or other portions of the basal ganglions was observed.

In conclusion, certain deductions may be drawn from observations on cases of verified traumatic intracerebral hemorrhage which are of value in the solution of this problem. Whether or not these principles are to be dignified as postulates, they at least rest on the solid basis of morbid anatomy. These principles regarding delayed traumatic hemorrhage may be stated as follows: 1. Hemorrhage into the brain after trauma may occur in young adults as well as in older persons. 2. Except for less common instances of laceration of the brain by direct injury, traumatic intracerebral hemorrhage is the result of the *coup-contrecoup* mechanism, the injury being sustained with the head in motion. 3. Clinical symptoms of the presence of hemorrhage usually become manifest within a few days, although the patient may survive for a considerable time. 4. The lesion is commonly found in the frontal or the temporo-occipital region and is relatively superficial rather than deep in the basal ganglions. (When the ganglionic region is involved, as it is at times in injury to the sides of the head, the lesions are usually small in the lenticular nucleus or more extensive in the external, not the internal, capsule.) 5. The hemorrhage may be primary, arising within the centrum, or secondary to severe contusions of the frontal or the temporal lobes. 6. Other signs of injury to the brain (such as contusions) are almost invariably present. 7. The lesion is commonly fatal, death being due to its presence or in part to other, associated traumatic lesions of the brain. In some instances recovery may take place on surgical evacuation of the clot if other severe lesions are not present.

Although, no doubt, exceptions to these rules may occur and atypical cases are encountered in which it may be difficult to make an absolute decision, in the great majority of instances, particularly when an opportunity is given to examine the brain, a definite conclusion can be reached as to whether the hemorrhage is truly of traumatic origin or is spontaneous.

SUMMARY AND CONCLUSIONS

In order to evaluate Bollinger's conception of delayed post-traumatic apoplexy, a study was made of some 38 cases of gross hemorrhage into the brain substance occurring as the direct result of trauma.

Except for 3 cases of gross hemorrhage resulting from direct laceration of the brain, a traumatic hemorrhage proved invariably to be a

typical *coup-contrecoup* effect of injury, in which the head in motion struck an immobile or relatively immobile object.

Two varieties of traumatic intracerebral hemorrhage are described. The first type is adjacent, or secondary, hemorrhage which is a part of a contusion of the temporal and frontal lobes which provokes it and is of no special clinical significance. The second variety is primary, or central, hemorrhage occurring in the centrum of the frontal or temporal lobes (rarely, in the less extensive form, in the external capsule and the ventricular nucleus). Central hemorrhages of the frontal and temporal lobes may reach such proportions as to assume clinical importance.

Such hemorrhages, particularly those occurring in the temporal or temporo-occipital centrum, become manifest clinically after an interval of lucidity or may pursue a progressive course in a patient who has never been rendered entirely unconscious. In such cases the clinical course mimics closely that of interval dural hemorrhages. When such hemorrhages are excessive, ultimate rupture into the ventricles or into the subdural space seems to be the rule. In the latter instance these subdural accumulations of blood may be mistaken for primary subdural hemorrhages.

Hemorrhages into the region of the basal ganglions following trauma apparently are limited to small hemorrhages occupying slitlike cavities in the external capsule or to small globular hemorrhages into the globus pallidus (the lenticular nucleus). No example of gross hemorrhage into the posterior limb of the internal capsule, such as appears spontaneously in cases of hypertension or arteriosclerosis, has been observed by us. It may, therefore, be safely assumed that gross hemorrhage in this region is not the result of trauma, for, of all portions of the brain presenting evidences of injury, this particular region seems to be most notably free.

Arteriosclerosis in itself does not seem to play an important part in the production of these hemorrhages, although it may have mild predisposing influence. There seems to be no greater incidence of gross intracerebral hemorrhage in persons with advanced arteriosclerosis and associated severe injuries than in younger adults. Other, rarer conditions, such as hypoplasia of the arteries or other vascular disease, may play a minor role in the production of post-traumatic hemorrhages. As far as our experience goes, syphilis seems to be of no influence whatever as a predisposing factor in the production of immediate or delayed hemorrhages.

The basic principles by which presumed instances of delayed traumatic hemorrhage are to be evaluated are briefly outlined.

EWING'S SARCOMA (ENDOTHELIAL MYELOMA)

J. F. HAMILTON, M.D.
MEMPHIS, TENN.

The subject of Ewing's sarcoma continues to hold the interest of the medical profession, especially of those members of it who see more than the casual patient with the disease. There are several reasons for this: (1) difficulties in diagnosis, since clinically and roentgenographically the tumor closely resembles other pathologic entities; (2) the fact that the cause is still obscure; (3) the fact that the mortality rate is excessive, and (4) the fact that present methods of treatment are deplorably ineffective. With these problems confronting them, physicians must disseminate the available information in an effort to reduce errors in diagnosis and must constantly strive to make earlier diagnoses. In order to accomplish these objectives, it is essential, first, that the physician inform himself better of the nature and behavior of Ewing's sarcoma and, second, that the lay public be impressed with the necessity of seeking early medical advice concerning symptoms referable especially to the extremities, particularly of persons between the ages of 5 and 20 years. Finally, the search for an ideal method of treatment must be continued.

Prior to Ewing's [1] history-making announcement, in 1921, of the term "diffuse endothelioma of bone" to designate the tumor under discussion, which he believed to be a definite entity, many articles had appeared in the literature pertaining to this disease. Up to that time it had been referred to by many writers as "a small or large round-celled sarcoma." Gross,[2] in 1879, wrote a classic paper on the subject "Sarcoma of Long Bones." There can be no doubt that he referred, in some cases at least, to Ewing's sarcoma when he described a "central and subperiosteal round-celled sarcoma."

There are still too many errors in diagnosis to permit an accurate estimation of the number of cases of endothelial myeloma from reports in the literature. The report of the Bone Sarcoma Registry for October

Read at the Third International Cancer Congress, Atlantic City, N. J., Sept. 14, 1939.

1. Ewing, J.: Diffuse Endothelioma of Bone, Proc. New York Path. Soc. **21**:17, 1921.

2. Gross, S. W.: Sarcoma of the Long Bones, Based upon a Study of One Hundred and Sixty-Five Cases, Am. J. M. Sc. **78**:338, 1879.

1938 recorded 236 registered cases. Twenty-five of these were submitted from this clinic, and an additional 3 were submitted as cases of Ewing's sarcoma but were not so classified by the registry. One of the 3 (case 3, table 1) was unclassified; the committee suggested diagnoses of lymphosarcoma, myeloma, osteomyelitis and Ewing's tumor. The patient died four years after admission to the clinic and eight years after the onset of symptoms of intercurrent infection incident to metastasis to the spine, followed by paraplegia. The second case (case 20, table 1) was not classified officially, but the diagnosis was regarded as

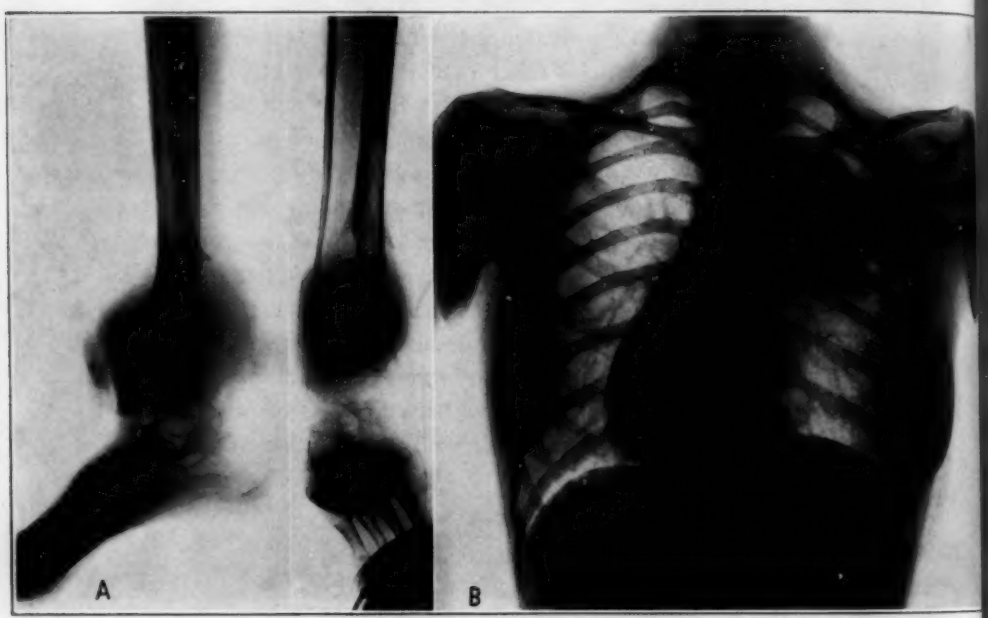

Fig. 1 (case 10, table 1).—*A*, anteroposterior and lateral roentgenograms taken May 20, 1931, showing partial destruction of the lower end of the tibia; lipping of the upper end of the tumor and fungating tumor growth through anterior and posterior wounds made for osteomyelitis. The patient, E. L., was 12 years of age. *B*, teleroentgenogram of the lungs taken July 10, 1939, eleven months after the first appearance of symptoms in the chest (over several years after the first admission, 5-20-31), showing a large tumor mass in the upper right lung field.

"chronic inflammation." The patient died two years later of an endothelial myeloma of the jaw with metastases to the lungs and liver. The third case (case 37, table 1) was classified as an example of osteogenic sarcoma; the opinion of the committee, however, was divided. The tumor regressed under roentgen therapy, but the patient died of metastasis to the head three and one-half months after admission. No report is available on 9 of the 28 cases submitted.

There is considerable confusion among writers regarding many phases of the endothelioma group of tumors in general and of bone tumors in particular. The endothelioma "dumping ground" has diminished to some extent, however, especially since Ewing described the tumor known

Fig. 2 (case 13, table 1).—Roentgenogram in the case of E. C., aged 12. The film, taken Dec. 29, 1933, shows condensation and destruction of the tibial cortex with lipping and radiating new bone.

by his name. He divided endothelioma into three types: (1) multiple endothelioma; (2) solitary angioendothelioma, and (3) diffuse endothelioma, or Ewing's sarcoma. The original Sarcoma Registry classification embraced only two types: (1) angioendothelioma and (2)

TABLE 1.—*Data on Twenty-Nine Cases of Ewing's Sarcoma and Eight Cases of Probable Ewing's Sarcoma*

No.	Patient	Admission, Date	Age	Sex	Symptoms and Comment	Duration of Symptoms	Site	Operation for Osteomyelitis	Trauma	Physical Findings	Roentgen Findings	Sarcoma Registry: Diagnosis	Sarcoma Registry: Committee Opinion	Treatment	Duration of Tumor: After Admission	Duration of Tumor: Total
1	E. R.	2/ 2/27	7	F	Pain; fever; tumor	6 months	L. fibula, lower ⅓	No	Yes	Swelling above	Osteolysis, onion peel	Ewing's sarcoma	Agreed	Roentgen therapy	Died; 3 years, 5 months	3 years, 11 months
2	A. L. M.	2/17/27	47	M	Pain; tumor	1 year	R. tibia, lower ⅓	No	No	Tumor ankle	Osteolysis, onion peel	Ewing's sarcoma	Agreed	Amputation, 2/18/27	Living; 8 years, 3 months	9 years, 3 months
3	I. N. D.	7/ 9/27	51	F	Pain; tumor	4 years	L. tibia, upper ⅓	No	No	Swelling knee; tenderness, upper tibia	Condensation	Unclassified	Lymphosarcoma; myeloma; osteomyelitis	Drainage, 7/16/27; excision, 1/11/28; roentgen therapy	Died; 4 years	8 years
4	S. C. S.	10/18/28	13	F	Pain; limp; fever; mass in groin	8 months	L. ilium, lower ½	No	No	Firm, tender mass above pelvic brim	Osteolysis	Ewing's sarcoma	Agreed	Roentgen therapy	Died; 7 months	1 year, 3 months
5	B. A. W.	1/13/29	16	M	Pain; swelling	6 months	L. tibia, middle ⅓	No	No	Firm, tender mass	Condensation, osteolysis	Ewing's sarcoma	Agreed	Roentgen therapy	Died; 5 months	11 months
6	E. S.	2/14/30	13	F	Pain	1 year	L. femur, lower ⅓	Yes, 2	No	Tumor; 2 operative scars	Osteolysis, onion peel	Ewing's sarcoma	Agreed	Amputation, 2/15/30	Died; 1 year, 6 months	2 years, 6 months
7	R. H.	7/25/30	52	F	Pain; tumor	3 years	R. tibia, middle ⅓	No	No	Firm, tender mass	Condensation	Ewing's sarcoma	Melanoma; carcinoma; sarcoma	Amputation, 8/1/30	Died; 5 months	3 years, 5 months
8	J. O. T.	8/ 3/30	21	M	Pain; fever	4 months	R. tibia, middle ⅓	Yes	No	Swelling	Condensation	Ewing's sarcoma	Ewing's sarcoma; osteomyelitis	X-ray; Coley's toxins, 18 months	Living; 9 years	9 years, 4 months
9	W. W. M.	8/29/30	39	M	Pain; soreness in left groin	1 year	L. pubis	No	Yes	Firm, tender mass	Osteolysis, pathologic fracture	Ewing's sarcoma	Agreed	Excision, 9/1/30; roentgen therapy	Died; 8 months	1 year, 8 months
10	E. L.	5/20/31	12	F	Pain; swelling	2 years	L. tibia, lower ⅓	Yes, 2	No	Fungating tumors, anterior and posterior	Osteolysis, onion peel	Ewing's sarcoma	Ewing's sarcoma; osteogenic sarcoma	Amputation, 5/20/31: roentgen therapy; Coley's toxins, 6 months	Living; 8 years; metastasis to lung 1 year ago	10 years
11	W. T. S.	7/11/32	20	F	Recurrent pain	1 year	R. tibia, middle ⅓	No	No	Tenderness	Condensation	Ewing's sarcoma	Agreed	Amputation, 2/14/33; roentgen therapy	Died; 1 year, 8 months	2 years, 8 months
12	E. G.	11/21/32	16	M	Pain in leg, knee and thigh; fever	5 months	L. femur, neck and upper ⅓	No	No	Mass, upper ⅓ of thigh	Osteolysis, onion peel, pathologic fracture	Ewing's sarcoma	Agreed	Roentgen therapy; Coley's toxins 4½ months	Died: 11 months	1 year, 4 months
13	E. C.	12/29/33	12	M	Tumor; roentgen therapy	2 years	R. tibia, upper ⅓	No	Yes	Firm, tender mass	Condensation, onion peel, sunray, erosion	Ewing's sarcoma	Agreed	Amputation, 12/29/33; Coley's toxins (20 doses)	Living; 6 years	8 years

13	E. O.	12/29/33	12	M	Tumor; roentgen therapy	2 years	R. tibia, upper ⅓	No	Yes	Firm, tender mass	Condensation, onion peel, sunray, erosion	Ewing's sarcoma	Agreed	Amputation, 12/29/33; Coley's toxins (20 doses)	Living; 6 years	8 years
14	E. H.	3/24/34	10	F	Pain; tumor; fever; loss of weight	5 months	R. 7th rib	No	No	Tumor, R. axilla	Osteolysis	Ewing's sarcoma	Agreed	Roentgen therapy	Died; 1 year	1 year, 5 months
15	M. B.	1/15/35	20	F	Recurrent rheumatism; pathologic fracture August 1933; continuous pain; mass	3¼ years 8 months	L. humerus, upper ⅓	No	No	Visible tumor	Osteolysis, onion peel	Ewing's sarcoma	Agreed	Coley's toxins 10 months; resection, 6/15/36	Died; 2 years, 3 months	5½ years
16	J. S.	3/26/35	11	M	Pain; tumor	2 years	L. humerus, middle and lower ⅓	No	Yes	Large fusiform tumor	Condensation, onion peel, sunray	Ewing's sarcoma	Agreed	Amputation, 4/1/35; roentgen therapy	Died; 11 months	2 years, 11 months
17	A. S.	6/12/35	12	M	Pain; fever; swelling	5 months	L. calcaneus	No	Yes	Swelling, ankle and heel	Condensation	Ewing's sarcoma	Agreed	Amputation, 9/9/35; roentgen therapy	Died; 1 year, 2 months	1 year, 7 months
18	H. G.	10/29/35	24	M	Resection 4 ribs August 1932; roentgen therapy; pain, swelling of R. thigh	4 years 1 year	6th to 9th ribs, R.; R. femur, upper ⅓	No	No	Swelling, upper ⅓ of thigh	Condensation, osteolysis	Ewing's sarcoma	Agreed	Roentgen therapy; Coley's toxins 3 months	Died; 1 year, 9 months	5 years, 9 months
19	J. G. W.	8/ 7/36	11	M	Pain in R. hip; fever; biopsy, October 1935; diagnosis, sarcoma; roentgen therapy	1 year	R. ilium	No	No	Firm mass	Condensation	Ewing's sarcoma	No report	Roentgen therapy	Died; 8 months	1 year, 8 months
20	C. K.	4/ 6/37	17	M	Pain, swelling; abscessed teeth 4 years previously	4 weeks	R. mandible	Yes	No	Swelling, R. gum; draining sinus	Osteolysis	Chronic inflammation	No report	Curettage; roentgen therapy	Died; 2 years; 1 month	5 years, 1 month
21	B. J. B.	5/13/37	6	F	Pain, tumor	6 months	L. tibia, upper ⅔	Yes, 2	Yes	Nodular, infected tumor, upper ⅓ of L. leg	Osteolysis, onion peel, sunray	Ewing's sarcoma	No report	Amputation, 7/2/37; roentgen therapy	Died; 7 months	1 year, 1 month
22	J. M.	6/14/37	22	F	Tender swelling in L. axilla; roentgen therapy; regression	6 months	L. 10th rib	No	No	Tender swelling over 8th to 10th ribs	Osteolysis, onion peel; metastasis to lung	Ewing's sarcoma	No report	Roentgen therapy	Died; 3 months	9 months
23	J. E. S.	9/ 3/37	21	M	Tumor; roentgen therapy, regression	8 months	L. tibia, middle ⅓	No	No	Firm mass	Condensation	Ewing's sarcoma	No report	Amputation, 9/6/37; roentgen therapy; Coley's toxins, 18 weeks	Died; 1 year	1 year, 8 months
24	J. M. W.	9/15/37	4	F	Pain; limp; fever; swelling; biopsy 1 year previously	2½ years	R. tibia, upper ⅔	No	No	Fusiform swelling	Osteolysis, onion peel, sunray	Ewing's sarcoma	No report	Amputation, 9/18/37; roentgen therapy	Died; 1 year, 2 months	3 years, 8 months
25	B. P.	10/23/37	19	F	Pain in L. knee, ilium	2½ years	L. ilium, posterior aspect	No	No	Firm, tender mass	Osteolysis with ostosis	Ewing's sarcoma	No report	Roentgen therapy	Died; 4 months	2 years, 10 months

TABLE 1.—*Data on Twenty-Nine Cases of Ewing's Sarcoma and Eight Cases of Probable Ewing's Sarcoma—Continued*

No.	Patient	Admission, Date	Age	Sex	Symptoms and Comment	Duration of Symptoms	Site	Operation for Osteomyelitis	Trauma	Physical Findings	Roentgen Findings	Sarcoma Registry: Diagnosis	Sarcoma Registry: Committee Opinion	Treatment	Duration of Tumor: After Admission	Duration of Tumor: Total
26	W. A. F.	1/ 7/38	47	F	Pain in R. knee	4 months	R. femur, lower ⅓	No	No	Slight tenderness, R. knee	Osteolysis	Ewing's sarcoma	No report	Amputation, 2/16/38; roentgen therapy	Died; 6 months	10 months
27	L. M.	7/ 8/37	15	F	Pain; loss of weight	9 months	Sacrum	No	No	Firm, tender mass	Osteolysis	Ewing's sarcoma	No report	Roentgen therapy	Died; 1 year, 3 months	2 years
28	M. H.	12/28/38	30	F	Pain; tumor; fever; radium and roentgen therapy	3½ years	R. femur, middle ⅓	Yes	No	Tenderness, lower ⅔ of thigh; old operative scar	Condensation, sunray, erosion	.....	.....	Roentgen and radium therapy; amputation, 1/2/39	Living; 8 months	4 years, 2 months
29	H. S. (Negro) John Gaston Hospital	2/26/37	11	M	Pain; swelling fever	4 months	Mandible	No	No	Swelling incisor region	Osteolysis	.....	.....	Excision, 2/23/37	Died; 4 months	8 months
										Probable Ewing's Sarcoma						
30	G. F.	5/24/21	13	M	Pain; fever	4 months	R. femur, upper ⅓	No	No	Firm, tender mass	Osteolysis, onion peel	.....	.....	Amputation, 5/26/21	.....	.....
31	M. L. L.	2/10/23	7	F	Pain; swelling, L. knee and thigh	3 months	L. femur, lower ⅓	No	No	Fusiform swelling	Osteolysis, onion peel	.....	.....	Amputation, 2/14/23	Died; 6 months	9 months
32	J. B.	10/30/23	15	F	Pain; fever	3 months	R. femur, upper ⅓	No	Yes	Swelling	.....	.....	.....	None	Died; 4 months	7 months
33	I. C.	11/15/26	14	M	Pain; fever	4 months	R. femur, upper ⅓	Yes	No	Swelling	Osteolysis, onion peel	.....	.....	Drainage	Died; 4 months	8 months
34	L. L.	5/23/27	6	M	Pain; swelling	1 month	L. femur, lower ⅓	No	Yes	Swelling	Osteolysis, onion peel	.....	.....	Amputation, 7/1/27	Died; 10 months	11 months
35	A. C.	2/ 8/32	17	F	Pain in back and legs	6 months	1st and 2d L. vertebrae	No	Yes	Slight kyphosis; tenderness, 2d lumbar vertebra; partial paraplegia	Negative	.....	.....	Laminectomy; roentgen therapy	Living; 7 years, 6 months	8 years
36	N. H.	7/ 9/35	21	M	Pain; swelling right thigh; drainage, Oct. 1934; roentgen therapy; regression	2 years	R. ischium	Yes	No	Swelling	Condensation, periosteal reaction; metastasis to lung	.....	.....	.....	Died; 2 months	2 years 2 months
37	L. A.	9/10/34	13	F	Pain; swelling	3 months	L. ilium	No	No	Swelling	Osteolysis	Osteogenic sarcoma	Osteogenic sarcoma; metastatic tumor	Roentgen therapy; Coley's toxins	Died; 4 months	7 months

diffuse endothelioma. In the revised classification of the registry for 1939 the aforementioned grouping was not changed. In a recent article, however, Ewing [3] stated:

> According to the present available observations, it seems desirable to recognize a special class of bone tumors arising from blood vessels with varying structure and degrees of malignancy as follows:
>
> A. Cavernous angioma.
>
> B. Plexiform angioma (sun-ray radiological type).
>
> C. Angio-endothelioma with fine blood channels lined by single rows of endothelial cells.
>
> D. Diffuse endothelioma, with pseudorosettes and perithelial units (Ewing's sarcoma).

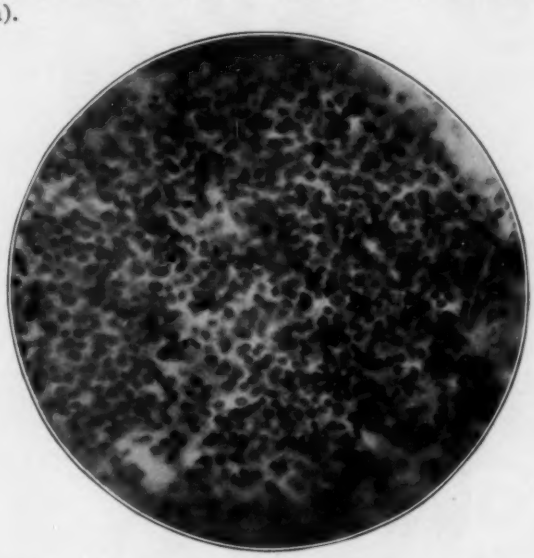

Fig. 3.—Photomicrograph of the tumor of E. C. (fig. 2), showing a solid sheet of cells. The cytoplasm is not shown; the nuclei are small, oval to round and moderately deeply stained. Nucleoli and mitoses are present. × 430.

The gross appearance of the tumor varies, of course, according to its age, its location and the character of its blood supply. The subperiosteal tumor, if examined before extensive hemorrhage and necrosis have occurred, is firm, rubber-like and covered by a capsule. Its cut surface appears moist, grayish white and semitranslucent; it is divided into lobules by connective tissue trabeculae and tends to well out. In the presence of necrosis, bone lysis and hemorrhage, on the contrary, the tumor has no form and may closely resemble purulent exudate. This type is commonly observed in the flat bones.

3. Ewing, J.: A Review of the Classification of Bone Tumors, Surg., Gynec. & Obst. **68**:971, 1939.

Ewing has stated that when microscopic study of a tumor reveals cells in sheets without intercellular stroma, usually with small vesicular nuclei, the cells often enclosing small or large blood spaces which contain intact and apparently circulating blood, one is justified in making a

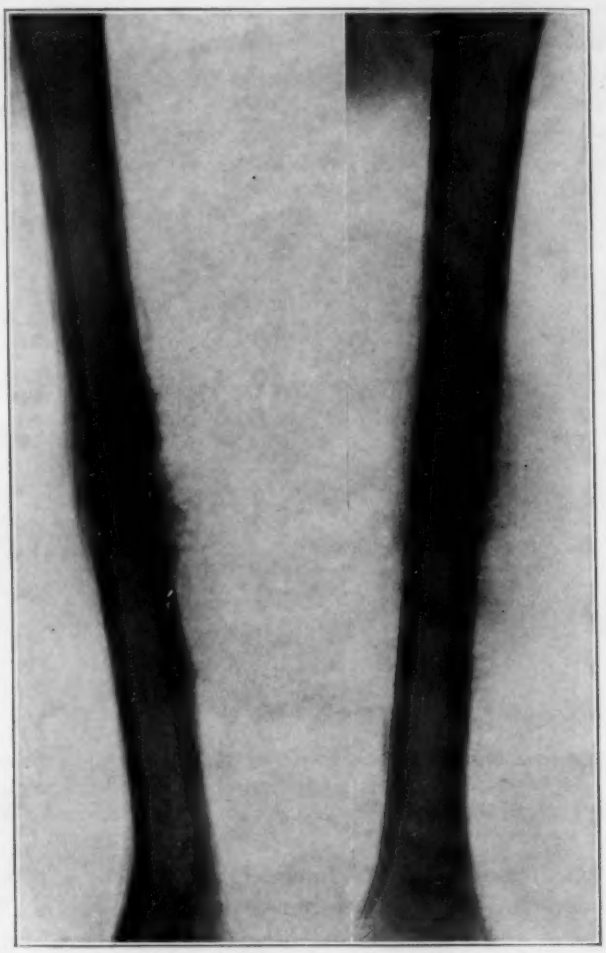

Fig. 4 (case 16, table 1).—Roentgenogram in the case of J. S. Jr., aged 11. The left humerus (March 27, 1935) shows condensation and destruction of the cortex, parallel and perpendicular new bone formation and infiltration of the soft tissues.

diagnosis of endothelioma. The vast majority of the tumors of our series were of this type. The usual microscopic appearance was that of solid, compact sheets of polyhedral cells with small, moderately

stained vesicular nuclei of fairly uniform size and round or oval shape. The limiting membrane of the nucleus was well outlined. The chromatin was finely granular, though chromatin knots were often seen. It is impossible to state whether some of these chromatin knots were not in reality nucleoli. The cytoplasm was scarce and when stained (hematoxylin and eosin) was neutral to acidophilic. In several of the specimens removed at some time after an operation for osteomyelitis, however, the nuclei of the cells were much larger and more vesicular and contained large chromatin knots or nucleoli. In case 8 (table 1), for example, the nuclei were so large that I regarded the tumor as an osteogenic sarcoma

Fig. 5.—Photomicrograph of tumor of J. S. Jr. (fig. 4), showing tumor cells in the vascular spaces between new bone spicules. The circled area is shown in figure 6 *A*. × 100.

until a decided and lasting response to roentgen therapy convinced me of my error. Thus, it is important that the pathologist keep in mind the pleomorphic character of some biopsy specimens, particularly those taken after a previous operation.

The origin of Ewing's sarcoma is still questionable; what is known regarding its histogenesis is based on conjecture. Melnick[4] and Oberling and Raileanu have stated that the tumor arises from undifferentiated

4. Melnick, P. J.: Histogenesis of Ewing's Sarcoma of Bone, Am. J. Cancer **19**:353, 1933.

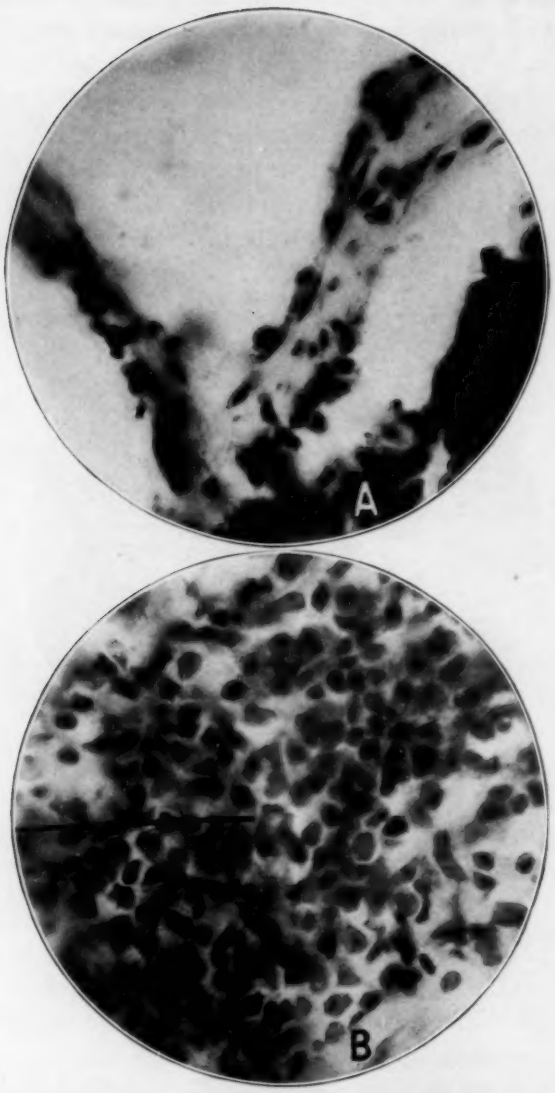

Fig. 6.—*A*, photomicrograph of the circled area in figure 5, showing tumor cells which appear to be forming a lining for the vascular spaces. × 1,000. *B*, photomicrograph (same case) showing a solid sheet of polyhedryal cells. The nuclei are irregular in size and shape and are moderately deeply stained. There is an occasional nucleolus and mitotic figure. The cytoplasm is palely stained. There is no intercellular stroma. × 1,000.

embryonic mesenchymal cells about the blood vessels in the haversian canals. Connor [5] and Ewing [6] at first believed that the disease arose in the marrow cavity. Ewing qualified his opinion, however, by stating that it begins in the blood vessels of the bone tissue. He further

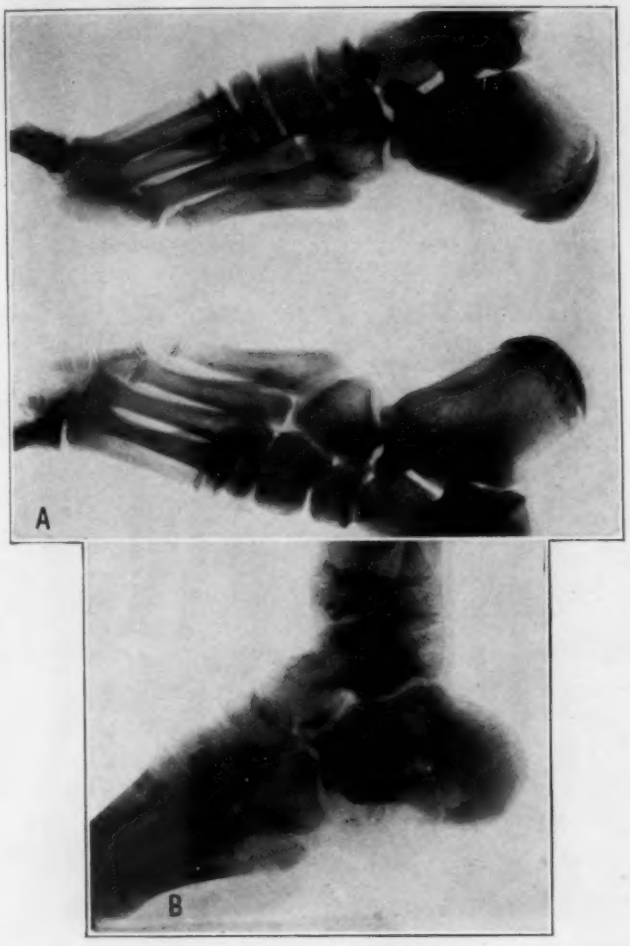

Fig. 7 (case 17, table 1).—*A*, roentgenogram in the case of A. S., aged 12. The film, taken June 12, 1935, shows increased density (probably the earliest roentgen change to Ewing's sarcoma) of the right calcaneus. *B*, roentgenogram taken on August 26, showing a destructive osteomyelitis-like lesion of the right calcaneus.

5. Connor, C. L.: Endothelial Myeloma, Ewing: Report of Fifty-Four Cases, Arch. Surg. **12**:789 (April) 1926; A Further Consideration of Ewing's Sarcoma. Am. J. Cancer **22**:41, 1934.

(Footnotes continued on next page)

explained that the tumor seems to originate in the perivascular lymph spaces and to be derived from the perivascular endothelium. I have observed the tumor cells within vascular spaces in several of my cases

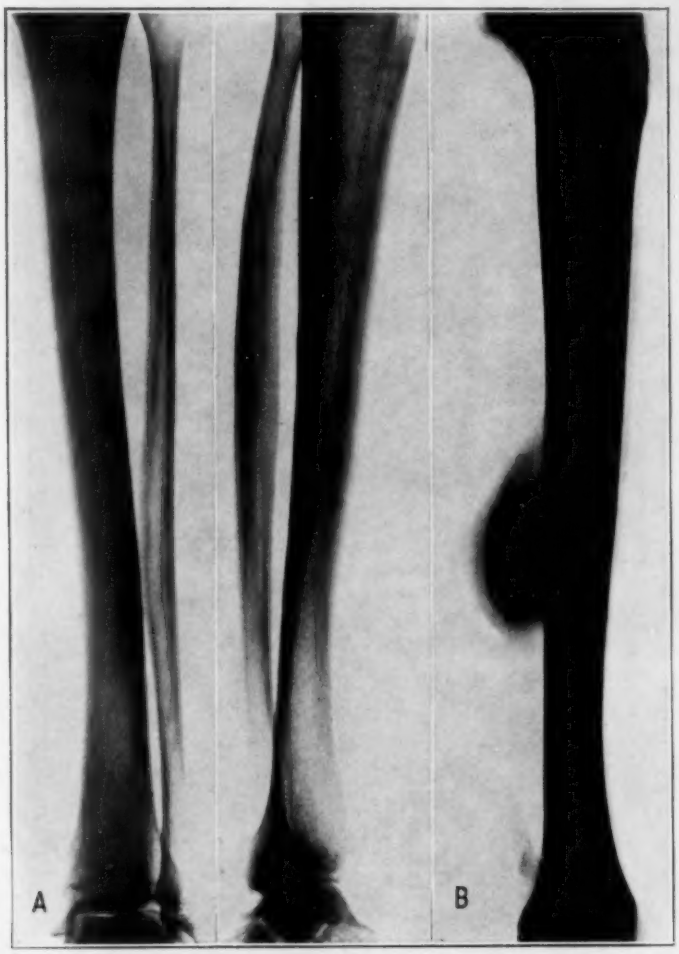

Fig. 8 (case 23, table 1).—*A*, roentgenogram in the case of J. S., aged 21. The film, taken Sept. 3, 1937, shows condensation of the cortex of the middle third of the left tibia. *B*, roentgenogram in the same case, showing the specimen after the soft tissues had been removed. The tumor is attached to the tibia. Note also a cordlike growth of the tumor which followed the course of the tibial tendon to ankle.

6. Ewing, J.: Further Report on Endothelial Myeloma of Bone, Proc. New York Path. Soc. **24**:93, 1924; Endothelioma, in Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 328; footnotes 1 and 3.

(cases 17 and 18, table 1). Malignant cells have been observed, apparently lining the spaces. Geschickter and Copeland [7] also concluded that the growth arises from lymphatic endothelium but attributed to it an intracortical or subperiosteal origin, while Kolodny [8] regarded the tumor as developing from the coalescence of multiple foci in the medulla and cortex. That Ewing's sarcoma may be of multiple origin has not been disproved. Indeed, Ewing himself stated: "It is difficult to determine whether the multiple tumors which are found, as indicated by clinical signs and radiographs, are metastases or multiple primary tumors. I have been unable to reach any conclusion, but the very extensive distribution of tumors in the late stages and the comparative integrity of the other organs lead one to think that the dissemination of the disease is mainly from multiple primary tumors developing throughout the bony system." The tumor in case 26 (table 1) appeared to be of a multiple medullocortical origin. The first roentgenogram, made four months after pain was first experienced in the knee, revealed a worm-eaten appearance of the lower femoral metaphysis with extension to the epiphysis. The patient was 47 years old. An amputation was carried out through the upper third of the right thigh, far above any clinical or roentgen evidence of the tumor in the lower third. To my surprise, tumor cells were found in the marrow cavity, within 1 cm. of the distal amputated end. A course of roentgen therapy was immediately begun and was followed by disarticulation at the hip joint. The patient died of metastases to the opposite femur and elsewhere five and one-half months after the first amputation.

Colville and Willis [9] expressed the opinion that many of the growths classified as Ewing's sarcomas would, on careful investigation, prove to be metastases from neuroblastomas. Hirsch and Ryerson [10] stated the belief that Ewing's tumor has been confused with metastatic bronchogenic carcinoma of bone. These opinions may have some truth in them. Postmortem examination in 1 of my cases (case 15) revealed tumor tissue in the left adrenal gland. My associates and I do not believe, however, that this tumor arose in the adrenal gland; our reasons for this opinion were explained in a report of the case.[11] Furthermore,

7. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, ed. 2, New York, American Journal of Cancer, 1936.

8. Kolodny, A.: Bone Sarcoma: The Primary Malignant Tumors of Bone and the Giant-Cell Tumor, Surg., Gynec. & Obst. (supp. 1) **44**:1, 1927.

9. Colville, H. C., and Willis, R. A.: Neuroblastoma Metastases in Bone, with a Criticism of Ewing's Endothelioma, Am. J. Path. **9**:421, 1933.

10. Hirsch, E. F., and Ryerson, E. W.: Metastases of the Bone in Primary Carcinoma of the Lung, Arch. Surg. **16**:1 (Jan., pt. 1) 1928.

11. Campbell, W. C., and Hamilton, J. F.: Endothelial Myeloma: Case Report with Necropsy, J. Bone & Joint Surg. **20**:1019, 1938.

too many postmortem reports have been made of Ewing's sarcoma without involvement of the adrenal glands to permit any question of the existence of this tumor. Studies of many microscopic sections made from blocks of tumor in cases 11, 13, 16, 17, 23 and 24 (table 1) incline one to believe that the tumor arises in the perivascular lymph vessels, provided, of course, that it has a single primary origin.

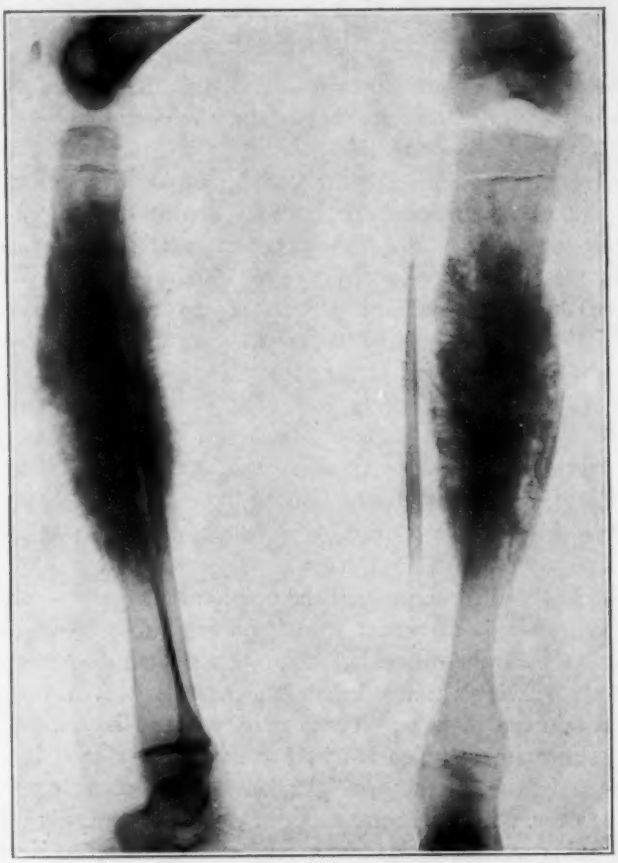

Fig. 9 (case 24, table 1).—Roentgenogram in the case of J. W., aged 4 years. The film, taken Sept. 15, 1937, shows a fusiform tumor of the right tibia with lipping and marked perpendicular striation of reactive bone. The general outline of the tibia is well preserved.

In this connection, Geschickter and Copeland referred to Ewing's sarcoma of the soft parts adjacent to the periosteum. I have observed 2 cases of fibrosarcoma arising from the soft tissues of the thigh in which the cytologic picture closely resembled that of endothelial myeloma. These cases are not included in the group reported.

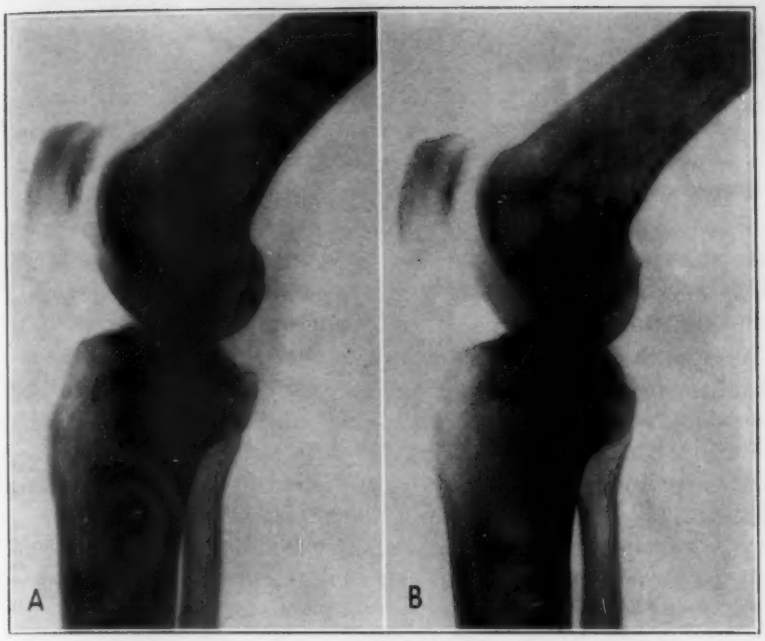

Fig. 10 (case 26, table 1).—*A*, roentgenogram in the case of W. F., aged 47. The film, taken Jan. 7, 1938, shows a mottled destructive lesion of the medulla and cortical portions of the lower third of the right femur without periosteal reaction. *B*, roentgenogram (same case) taken January 31, shows slightly more destruction of bone than is observed in *A*.

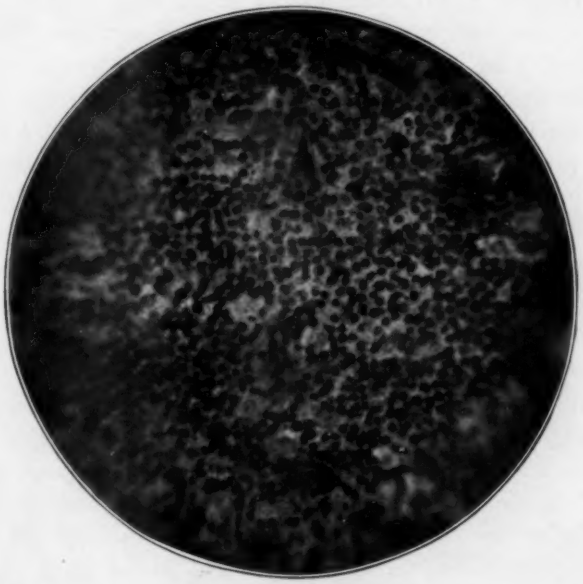

Fig. 11.—Photomicrograph of the tumor of W. F. (fig. 10), revealing a solid sheet of tumor cells. The nuclei are round to oval, fairly uniform in size and moderately deeply stained. The cytoplasm is not visible. Mitoses are present. There is no intercellular stroma. × 430.

The cause of Ewing's sarcoma, like its site of origin, is unknown. In my opinion, the theory of embryogenic disturbance, whether chemical or hormonal, is as well founded as the theories of an infectious or traumatic cause.

The diagnosis must rest on a carefully taken history, attention being given to details, and on the physical, roentgen and pathologic findings. Every patient should be closely studied with the following signs and symptoms in mind.

Intermittent attacks of pain, with or without swelling and fever, in a flat bone or in the shaft of a long bone, lasting in the beginning only a few days to a week or two, with the intervals between attacks gradually becoming shorter until the patient is forced to seek medical advice, are highly suggestive of Ewing's sarcoma. Especially is this true of persons less than 20 years of age. During the remissions the patient may feel entirely well and may have normal use of the affected part. The growth of the tumor may be so insidious that advanced changes may be observed in the first roentgenogram of the bone. Indeed, a pathologic fracture may take place before the patient comes for roentgen study. A case in point was case 15 (table 1).

The pain may be explained on the basis of intraosseous or subperiosteal pressure from growth of the tumor or from hemorrhage. I have found no suggestion in the literature of the probability that hemorrhage may be responsible for the pain. This, however, is quite likely, particularly in the acute attacks of the early stages. Moreover, hemorrhage may well cause the fever and leukocytosis. The patients have no fever or leukocytosis during the painless intervals of the clinical course, even though the tumor continues growing, whereas a leukocyte count of from 12,000 to 15,000 per cubic millimeter may be found during an attack of acute pain and fever. Leukocytosis with little, if any, alteration in the differential blood count may be of some significance. Such a blood picture has been observed, though in too few patients to permit any conclusion. This type of hemogram is not consistent with the infectious theory of histogenesis.

All of our patients had a negative Wassermann reaction. No Bence Jones bodies were found in any of the urinalyses.

Loss of weight and appetite are late manifestations of the disease. The pulse rate is believed to be accelerated so long as growth of the tumor is active. This has proved a valuable prognostic sign in my experience, leading me to suspect concealed metastases, especially in patients who return for observation after initial therapy. If the tumor is in the shaft of a long bone, a firm, fixed tender mass may or may not be palpable; soft tissue reaction and swelling may obscure the tumor,

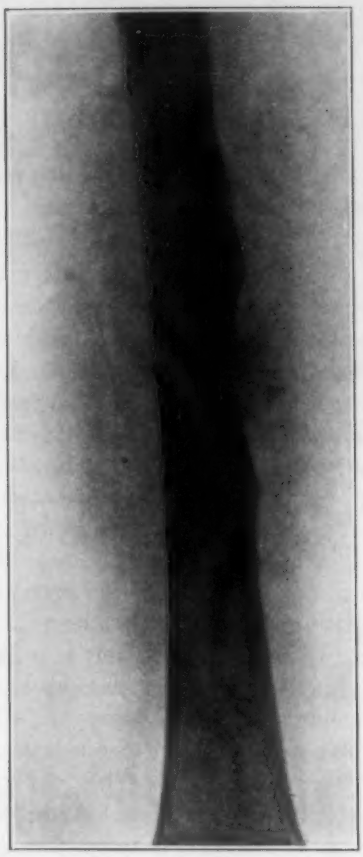

Fig. 12 (case 28, table 1).—Roentgenogram in the case of M. H., aged 30. The right femur (Dec. 28, 1938) reveals condensation, destruction and spicules of reactive bone.

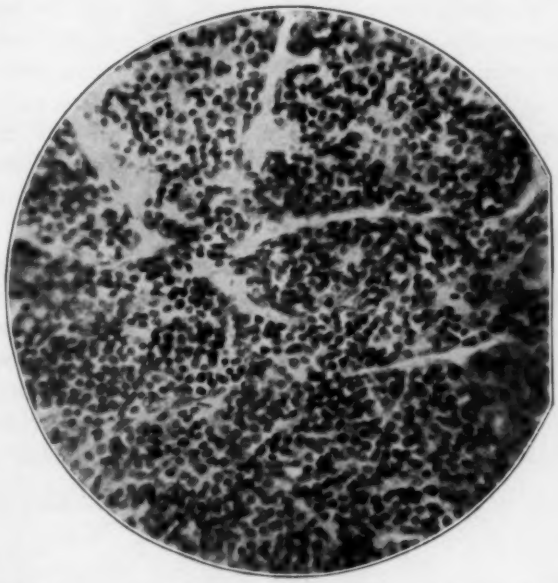

Fig. 13.—Photomicrograph of tumor of M. H. (fig. 12) reveals solid sheets of small round cells divided into lobules by fibrous connective tissue trabeculae. The nuclei are small, round to oval and fairly uniform in size. Cytoplasm is not visible. Mitoses are present. There is no intercellular stroma. × 430.

or only a questionable thickening of the shaft itself may be found. Fever is usually detected at the site of the tumor, and the superficial veins may be dilated and visible.

Roentgenograms are indispensable diagnostic agents. Condensation is the earliest roentgen evidence of Ewing's sarcoma; the involved bone reacts violently to the invasion of the disease process. This is a strong point in favor of a subperiosteal or intracortical rather than a medullary origin of the growth. Cases 8, 11, 13 and 23 (table 1) illustrate this compensatory bone reaction. In case 23 thickening and condensation were revealed by the roentgenogram, and on pathologic study of the entire circumference of the shaft of the tibia at the level of a small, elliptic subperiosteal tumor the marrow cavity was filled with a similar bone reaction. This reaction on the part of bone not only to Ewing's sarcoma but to other diseases, which makes diagnosis all the more confusing, has been known for years but was reemphasized by Campbell [12] as being especially apparent in young patients with this disease. He called attention to the three stages of osseous change manifested by the tumor in the roentgenogram: (1) condensation; (2) invasion, expansion, striation and destruction, and (3) disintegration of all bony structure and invasion of the soft tissues. This is probably the order of development of the growth in young bone. A number of years may be required for completion of the evolutionary pathologic process, or it may be completed within a few weeks to a few months.

I believe, with others, that the Ewing tumor cell has no part in the formation of bone. Connor,[5] however, stated that the parent cell of the tumor may differentiate into an osteoblast. Lipping (onion peel), so commonly seen near the junction of diseased and healthy bone in the late stage, is the remains of the parallel layers of reactive bone laid down at the time of invasion and expansion of the cortical and subcortical zones by the tumor. This is well illustrated in cases 1, 2, 6 and 10 (table 1). Radiating spicules of reactive bone lying perpendicular to the shaft, such as were found in cases 16 and 24 (table 1), are not uncommonly seen.

Some authors advocate the use of the therapeutic test by means of roentgen therapy to establish a diagnosis, regression of the tumor being highly suggestive of Ewing's sarcoma. One can imagine serious objections to this practice as a routine measure. If, however, one knew that taking a biopsy specimen would subject the patient to undue risk of metastatic spread and the technic of roentgen therapy were standardized, the therapeutic test might be justified, although scientific knowledge

12. Campbell, W. C.: Endothelial Myeloma, J. Bone & Joint Surg. **16**:761, 1934.

would suffer irreparably. The danger of spread of the tumor as a result of removal of a biopsy specimen is debatable. Some of the most eminent authorities frown on the procedure. There may be a few medical centers wherein opinion is sufficiently expert to diagnose and treat this disease without resorting to biopsy, but to endorse such a plan for general adoption would be hazardous. The time has not come when one may safely advise the sacrifice of a limb for a bone tumor which presents as many diagnostic pitfalls as Ewing's sarcoma without first having microscopic confirmation. Furthermore, the taking of biopsy specimens, particularly from this tumor, has not been proved, so far as I know, to be conducive to metastasis. McLean and Sugiura [13] performed "needle biopsies" of a number of rat carcinomas and mouse sarcomas and in some of the animals macerated the tumor with the needle. There was no increase of metastases over those observed in a control group.

Colville and Willis [9] expressed the opinion that a diagnosis of Ewing's sarcoma cannot be made by microscopic sections alone. Attempts to make a diagnosis from biopsy material are indeed exceedingly hazardous. This is true especially if the tissue is removed in small particles, if necrosis is present or if only the margin (edematous envelope) of the tumor is excised. If the biopsy specimen is taken from the edematous tissue adjacent to a subperiosteal elliptic type of tumor, for example, a few scattered tumor cells with more or less flattened nuclei, endothelial cells and lymphocytes may be found. Such a picture may be easily confused with inflammation. An unquestionable block of tumor tissue should be excised if the surgeon expects a rapid section diagnosis.

Ewing's sarcoma must be differentiated from (1) inflammation, (2) osteogenic sarcoma, (3) lymphosarcoma, (4) Hodgkin's disease and (5) retinoblastoma.

The roentgen appearance of the sclerosing osteomyelitis of Garre may be identical with that of Ewing's sarcoma. The presence of fever and changes in the blood and the fact that roentgen therapy may relieve pain are common to both. Biopsy and cultures will determine the diagnosis.

Syphilitic infection of the bone may produce the roentgen picture of Ewing's sarcoma; the lesions of the former, however, are often multiple in the tibia, clavicle and sternum. The age incidence of syphilis is usually beyond 30 years. The complement fixation test will differentiate the two conditions. If the reaction to the Wassermann test is positive and there is still doubt that the bone lesion is syphilitic, one should wait for the therapeutic test before taking a specimen for biopsy.

Osteogenic sarcoma is rarely seen in the shaft of the long bones. Its usual site is in the metaphysis, from which it tends to invade the

13. McLean, J., and Sugiura, K.: Does Aspiration Biopsy of Tumors Cause Distant Metastasis? J. Lab. & Clin. Med. **22**:1254, 1937.

epiphysis. The production of bone by the tumor is often obvious. In addition, the cortex is obliterated early in the course of the disease. The tumor, moreover, does not regress under roentgen or radium therapy. Recurrent pain and fever are uncommon, and the duration of symptoms usually is shorter. Microscopic examination seldom should offer any difficulty in the diagnosis.

Primary invasion of bone by lymphosarcoma is rare. The lesions are likely to be multiple. Periosteal reaction takes place late, if at all, considering the degree of bone destruction. Biopsy is the determining factor.

Hodgkin's disease must be distinguished from Ewing's sarcoma by microscopic examination.

Retinoblastoma may resemble Ewing's sarcoma clinically, roentgenographically and microscopically. It is exceedingly difficult, if not impossible, to differentiate the two conditions microscopically. The finding of true rosettes in retinoblastoma, although not always possible, especially in bone lesions, is a material aid; one must remember, however, that pseudorosettes may sometimes be found in Ewing's sarcoma. We have observed 2 patients with retinoblastoma within the past year. In both, the right eye had been enucleated approximately nine months before metastases appeared in the right ulna and the right scapula, respectively. The material from one of these tumors was reviewed by a distinguished pathologist in a large medical center, who made a diagnosis of Ewing's sarcoma. A portion of the same biopsy specimen was sent to the United States Army Medical Museum, where the eye had been sent nine months previously; the diagnosis from the museum was retinoblastoma with metastasis to the ulna. Both patients lived only a few months.

The prognosis in cases of Ewing's sarcoma, as in those of other malignant tumors, must be guarded. Experience would seem to indicate that the expression "a five year cure" is erroneous; to speak of "a ten year cure" probably would be more accurate. Cures usually are reported in 7.5 to 15 per cent of cases. Three, or 10 per cent, of my 28 patients whose cases were registered have lived five years or longer without a recurrence.

There is no known single or combined specific cure for the disease. Administration of Coley's toxins has been defended through the years by Coley and others [14] as a valuable therapeutic measure. Irradiation with roentgen rays and radium, followed by radical operation at the first

14. Coley, W. B.: Endothelial Myeloma or Ewing's Sarcoma, Radiology **16**:627, 1931; Endothelial Myeloma, or Ewing's Sarcoma, Tr. South. S. A. **43**:65, 1931; Endothelial Myeloma, Am. J. Surg. **27**:7, 1935.

evidence of a return of activity of the tumor, has been proposed by Ewing. Others feel that radical operation followed by irradiation is the procedure of choice, and according to statistics this is the most successful regimen. That endothelial myeloma regresses after irradiation is well known, but the clinical behavior of the tumor and the postmortem observations support the contention that irradiation alone is not curative. The clinical course and microscopic observations in case 15 (table 1) would seem to lend strength to this opinion. The patient in this case received a total of 15,900 roentgen units. On subsequent examination of the resected humerus, viable tumor cells were revealed in the marrow cavity. Groups of two or three suggestive-looking cells were scattered through the sections made from the soft tissue at the time of operation; that these were tumor cells was evidenced by the recurrence of the tumor about the fibular graft. Brunschwig [15] recently denied that Ewing's tumor cells are radiosensitive, since they are not entirely destroyed.

Geschickter and Copeland reported on 2 of a group of 30 patients living five years after treatment by irradiation, alone or with exploration; 3 of a total of 29 patients living five years after resection or amputation without irradiation, and 3 of 18 who were well five years after resection or amputation and irradiation. In a recent personal communication to me, Dr. Bowman C. Crowell, of the Bone Sarcoma Registry, stated that of the 236 registered patients with Ewing's sarcoma 14 have lived from five to twenty-one years after treatment. These were among a group of 164 who were treated five or more years ago. Thirteen of the 14 patients were subjected to operation. Eight underwent amputations, and in 3 the tumor was excised. Two were treated by resection and subsequent roentgen irradiation. Of the 8 who underwent amputations, 5 received Coley's toxins in addition, and 6, irradiation. Five of the 8 had undergone one or more surgical procedures prior to amputation. One of the 14 received roentgen therapy and Coley's toxins, without any operation other than removal of a biopsy specimen. One patient died of an unknown cause seven and one-half years after treatment.

Since 1920, 36 patients have been admitted to this clinic with a diagnosis of Ewing's sarcoma. Another case has been added from the records of the John Gaston Hospital, making a total of 37 cases (table 1). Of the 36 cases from the clinic, 16 (cases 1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 32, 33, 34 and 35), as well as 1 other not included in this series, were reported by Campbell in 1934.

15. Brunschwig, A.: Radioresistant Ewing's Sarcoma of Bone, Radiology **27**:328, 1936.

Some of the necessary data are lacking for making a definite diagnosis in 8 of the 37 cases listed in table 1, though the data available are sufficient to justify inclusion of these as probable Ewing's tumors. For analytic purposes, however, I am considering an analysis of only the 29 patients in whose cases biopsy material is available in addition to all other necessary data.

It is an interesting fact (table 2) that 15 (51.7 per cent) of the 29 patients were between 11 and 21 years of age; 19 (65.5 per cent), under 21 years of age, and 24 (82.7 per cent) under 31 years of age. Only 5

TABLE 2.—*Age and Sex Incidence of Ewing's Sarcoma*

Age	Number			Per Cent	
	Male	Female	Total		
1-10	..	4	4	13.8	65.5 / 82.7
11-20	8	7	15	51.7	
21-30	3	2	5	17.2	
31-40	1	..	1	3.4	
41-50	1	1	2	6.8	
51-60	..	2	2	6.8	
Total	13	16	29	100.0	

TABLE 3.—*Site of Primary Lesion of Ewing's Sarcoma*

Bone	Total Number of Cases	Upper Shaft	Lower Shaft	Mid-Shaft
Tibia	11	2	2	7
Femur	4	1	2	1
Ilium	3	..	..	..
Humerus	2	1	..	1
Rib	3	..	..	..
Mandible	2	..	..	..
Fibula	1	..	1	..
Pubis	1	..	..	..
Calcaneus	1	..	..	..
Sacrum	1	..	..	..

(17.2 per cent) were over 30 years of age. The youngest patient (case 24) was 4 years old when admitted but had had symptoms since the age of 1½ years. The oldest (case 7) was 52 years old when first seen; symptoms had been present for three years. The average duration of symptoms before admission in the group of 29 patients was seventeen and seven-tenths months; the shortest was four months, and the longest, forty-eight months.

Table 2 shows a sex incidence in the 29 cases of 13 males and 16 females.

A history of trauma was obtained in 6 (20 per cent) of the 29 patients. This is low compared to other statistics.

In table 3 may be seen the primary location of the tumor, as follows: tibia, 11 instances (36.6 per cent); femur, 4 instances (13.4 per cent);

ilium, 3 instances (10.3 per cent); rib, 3 instances (10.3 per cent); humerus and mandible, 2 instances each (6.9 per cent) and fibula, pubis, calcaneus and sacrum, 1 instance each (3.4 per cent). Of the 11 tumors of the tibia, 7 were in the middle third and 2 each in the upper and lower thirds. One of the tumors of the femur was in the middle third, and 2 each were in the upper and lower thirds. The 2 in the humerus were in the middle and upper thirds. The fibular tumor was in the lower third.

Five patients (cases 2, 8, 10, 13 and 28, table 1) of the 21 with a positive diagnosis of Ewing's sarcoma and 1 (case 35, table 1) of the group of 8 with a probable diagnosis of Ewing's sarcoma are living. The patient in case 2 when last heard from (1935) had lived nine years after amputation. The patient in case 8, who received irradiation and Coley's toxins, was also living nine years later. This case is most interesting. Drill holes had been made into the tibia for osteomyelitis three months before the patient's admission to this clinic. The symptoms returned. After admission a trap door was made in the tibia, for the same condition. Because of the pleomorphism and large cells observed in the biopsy specimen, I reported the presence of sarcoma, probably osteogenic. Since this was difficult for the surgeon to believe, two other biopsies were performed. The first of these specimens contained tumor cells, while the second contained none.

The patient in case 10 has lived eight years after amputation and treatment with roentgen rays and Coley's toxins. One year ago, however, seven years after operation, symptoms referable to the chest appeared. The roentgenogram disclosed a right pleural effusion and metastasis to the right lung. Irradiation is now being administered.

The patient in case 13 was living six years after amputation. The operation was both preceded and followed by irradiation, and, in addition, Coley's toxins were given postoperatively. Only nine months have elapsed since the patient in case 28 underwent an amputation. Roentgen and radium irradiation were carried out previously. The patient in case 35 of the group with probable Ewing's tumors is still living and states that she is well, seven and one-half years after admission and treatment by roentgen rays alone.

CONCLUSIONS

1. I believe that Ewing's sarcoma is a definite entity and that it is of vital interest to the medical profession for the following reasons: (*a*) diagnosis is difficult, since clinically and roentgenographically the tumor closely resembles other pathologic entities: (*b*) the cause is

obscure; (*c*) the mortality rate is excessive, and (*d*) present methods of treatment are deplorably ineffective.

2. There are several theories of the origin of Ewing's sarcoma. It is not impossible that the disease may have a multiple primary origin.

3. The cause of the tumor is unknown.

4. The gross and microscopic appearances of the tumor are variable.

5. The high incidence of the disease in persons between the ages of 5 and 20 years is noteworthy.

6. A careful history, physical examination and roentgen study are of first importance in the diagnosis.

7. The diagnosis must rest on correlation of all available data. Microscopic confirmation of the clinical and roentgen findings is essential, especially prior to radical operation.

8. Because of the similarity of Ewing's sarcoma to other pathologic entities, a differential diagnosis is often difficult.

9. One should recognize the osseous changes characteristic of different stages of the disease, as shown in the roentgenogram.

10. Properly selected biopsy material is necessary to a dependable microscopic diagnosis. Errors may easily occur from ill chosen material.

11. The prognosis must be guarded, even after five years.

12. No specific treatment is known to be curative. Evidence seems to indicate that radical operation followed by irradiation offers the most hopeful prospect for life.

Dr. J. G. McFetridge, associate pathologist, gave valuable assistance in the preparation of this paper.

CATGUT SUTURES AND LIGATURES

GREATER EFFICACY ACHIEVED THROUGH OBSERVANCE OF CERTAIN DETAILS

CYRUS F. HORINE, M.D.
BALTIMORE

"Good surgery is largely a matter of paying particular attention to little details."—J. M. T. Finney.

Through the centuries it has been known that twisted fibers are strong even though individually their component parts resist little tension. Notwithstanding, little attention has been paid to the matter of the twist in catgut suture material as it may affect the tensile strength and absorption of the strand and the reliability of the knot. It may safely be admited that some important and effective details in the practical use of catgut sutures and ligatures have been entirely overlooked. It is also to be admitted that surgeons have been rather careless in their use of catgut, and no doubt reckless with the truth in charging certain failures inadvertently to faulty material rather than to improper application.

The purpose of this article is to show how the twist and its variations can alter the tensile strength, the absorption of the strand and the reliability of knots. A preliminary presentation and review of the subject are given in another publication.[1]

EXPERIMENTAL DEMONSTRATION OF RELATION OF THE TWIST TO FRICTIONAL VALUES AND THE STRENGTH OF THE KNOT

In a simple experiment one may take a smooth, straight strand of catgut and carefully apply a large right hand throw (without acute bends or twists) to form a knot on the strand. When the two free ends are drawn taut, the loop gradually slides toward the right. There is little or no tendency for a loop made with a left hand throw to proceed to the right when the maneuver is carried out under similar conditions.

If one applies single right and left hand throws to a strand of nonboilable (hydrous) catgut and makes sufficient tension to break the knot, the right hand knot breaks first in the large majority of instances, as shown in the table. Various results are found when the test is applied to the anhydrous, or boilable, suture material. Variations of frictional

1. Horine, C. F.: Some Physical Factors Regarding Catgut Ligatures and Catgut Knots, to be published.

values in the wet and dry strands have been clearly demonstrated in the valuable work reported recently by Taylor.[2]

The tying of a knot, after all, is a matter of increasing the twist in the knot made with a right hand throw and decreasing the twist in the left hand knot, if the action is applied to the conventionally spun (clock-

Tests on Strength of Knots *

	00 Plain Catgut	No. 1 Chromic, 10 to 20 Day
Straight pull tests for control	6.04†	12.00
Single right throw knots	3.23	6.80
Single left throw knots	3.63	8.60
Single right throw knots over glass rod	6.65	11.71
Single left throw knots over glass rod	5.64	10.35

* The tests were made on catgut of three popular brands which had been bought on the open market. The results represent the averages (combined) of many hundred knots which had been broken. The proportional differences in the various knots compared well in the three different brands.

† All the figures represent pounds (1 lb. = 453.59 Gm.).

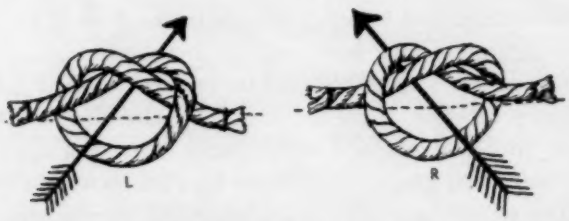

Fig. 1.—*L* shows a knot made by a left hand throw and *R* a knot made by a right hand throw. In *L* the horizontal axis forms an angle of approximately 135 degrees, as shown by the arrow; in *R* the horizontal axis forms an angle of approximately 45 degrees.

wise) hydrous, or nonboilable, material. However, other physical factors influence the degree and character of the torsion. The horizontal axis of the loop made with a right hand throw forms an angle of approximately 45 degrees; this angle decreases, as the loop is drawn to knot formation. The horizontal axis of the left hand loop forms an angle of approximately 135 degrees; this angle increases as the loop is drawn taut to form the knot (fig. 1). Variations of the vertical axes of the loops are also to be noted.

Tension applied to the strands in the tightening of the loop to knot formation reduces the areas of frictional surfaces, and the knots break at the converging points of tension and friction. In the loop formed by a right hand throw there is a shearing of the strand quite transversely to its long dimension at the point of acute angulation. The lesser fric-

2. Taylor, F. W.: Surgical Knots, Ann. Surg. **107**:458, 1938.

tion in the reduction of this loop to the "breaking knot" allows it to divide before the knot formed by the left hand throw in the test of the nonboilable, or hydrous, catgut. The test of the right hand knot with its acute twist and subsequent fracture of the strands demonstrated the clinical phenomenon in which small bits of tissue are tied under apparent low tension. Too frequently the surgeon has quickly and erroneously concluded that this is due to defective material, when actual tests would have shown evidence of adequate tensile strength "on the straight pull."

When one makes similar experiments by tying single right and left hand throws over a glass rod approximately ¼ inch (0.6 cm.) in diameter, greater resistance to tension occurs in the right hand loop than in the left hand one, providing the various crossed strands are drawn in their respective normal planes and angles. Furthermore, considerably more tension is withstood in these tests than in the experiments previously described; this difference is shown in the accompanying table.

CLINICAL APPLICATION

The varied and controverted figures giving results of experiments on the use of catgut suture material are due to variations in method of preparation and in manner of experimentation as well as to carelessness or indifference in clinical procedure. While there is no intent in this paper to continue the old discussion of the relative merits of catgut as compared with other suture substances, it may be said that it is rather remarkable that through years of controversy catgut has retained much popularity and withstood many erroneous criticisms of bad results.

A fair appraisal of catgut as suture material will be made after the material has been tried under more exacting practical conditions. Only after such trial can answers be given to the following questions: What is the effect of torsional variations on tensile strength? What is the effect of torsional variations on the absorption of the strand? How should the torsional variations be respected in the methods of application of sutures and knots?

Adequate tensile strength is given in the materials now produced by the reliable manufacturers. In the ultimate analysis, tensile strength either on the straight pull or in knot tests is not the all important point to be considered in the case of nonboilable catgut suture or ligature. The relationship of moisture to torsional variations in the strand needs further consideration for the production of more reliable material. This will be discussed in a future communication.

In the simple tests of single right and left hand knots on the same strand, the strand torsion is increased in the knot formed by the right hand throw and decreased in that formed by the left hand throw. There-

fore it may be expected that the loss of twist in the left hand knot should cause it to break before the right hand knot. However, with the same amount of tension applied to the two, the lesser friction on the component parts of the knot made by the right hand throw allows that knot to be drawn tighter, resulting in shearing of the strand. Surgeons should be mindful of these facts when small bits of tissue are tied, especially when the smaller materials are being used.

One of the most important factors in the general problem is the relationship of the twist to the hydrolysis and the absorption of the strand. The loss of the twist exposes more surfaces of the material to the effect of tissue juices or other agents. This was demonstrated in a previous paper. Sutures and knots should be so placed that the twist and the tensile strength are preserved. The consensus is that the square, or reef, knot is the best one. According to Taylor, triple throw square knots, tied flat, are the most reliable for catgut. No doubt many clinical observations substantiate this opinion.

Fig. 2.—Right and left hand throws producing the two forms of square, or reef, knots. *L* shows a square knot which is formed by using the left hand throw (counterclockwise, opposite to the twist in the material) as the original throw; *R* shows the square knot which is made by using the right hand throw (clockwise, the same direction as the twist) as the original one. The knot shown in *R* is the best type, and it should be used consistently in catgut ligatures. Triple throws are more reliable, and in each type of knot the third throw should be the reverse of the throw forming the second loop.

The Two Forms of Square Knots.—It is to be recognized that square, or reef, knots may be tied in two different forms with regard to the twist in the suture material: (1) In one form, the first throw of the knot is made to the right, the same direction as that of the twist in the conventionally spun material; while the second throw is made to the left, or counterclockwise, opposite to the direction of the twist, and if three throws are used, the third and final one should be applied in the right direction; (2) the second form is made by a reversal of the direction of all the throws just mentioned, a left hand throw being the initial one (fig. 2).

The first form, originating with the right hand throw, is the more efficient, and particularly so in the use of hydrous, or nonboilable, material of variable water content, torsion and friction coefficient. While it must be remembered that in the tying of tissues of smaller diameters, the loop made by the right hand, or original, throw in this first type of knot breaks more easily (especially in the smaller sizes of catgut) than that made by the left throw, nevertheless by careful use the required tension is obtained with minimum injury to the strand. Increased torsion rather than separation of fibers results. Strangulation of tissues and shearing of the strand are effected under extreme tension. At the same time, insufficient tension within the suture loop and fracture of the strands occur if the strands are tied in exaggerated horizontal and angulated positions. This original throw of the knot is the most important one, and sufficient tension can be obtained within the suture loop when wet catgut is used, with less likelihood of "slipping" while the second throw is being applied. The clockwise rotation of the strand in the right hand simultaneous with the counterclockwise rotation of the strand in the left hand during the act of tying this particular throw, as pointed out in the other article, already mentioned, gives better results if the catgut is large and heavily saturated with moisture.

The second, or left hand (counterclockwise), throw completes the knot. The second loop is drawn flat with sufficient tension to lock the first one, and it is important, as already emphasized, that the strands should be drawn with the horizontal axis of the loop in an angle of approximately 135 degrees. In view of the fact that the direction of this throw is opposite to the torsional direction in the strand, one can close the loop with less tension by increasing the counterclockwise rotation of the crossed strands as they are being drawn taut. However, this is not to be recommended unless one is quite sure that the first throw has remained securely tied. Otherwise, if this unwound portion slides reversely through to become the areas adjacent to the knot, premature absorption occurs at these sites because of this loss of twist. Increased clockwise rotation of the strands during the act of tying a left hand throw increases the difficulty of tying the knot securely.

The third, and final, throw of the knot is carried out as described in the paragraph on the original right hand throw.

Vertical and Horizontal Rotations of Knots and Sutures.—Surgeons, pathologists particularly, may have noted at autopsy that few square knots previously tied flat remain in this state. A partial explanation of this may be gained by consideration of the rotation of the knot proper and the rotation of the suspended loop portion of the suture. Pressure due to absorption of moisture causes the material to rotate in the counter-

clockwise direction in its attempt to straighten. A suspended loop of a suture under slight tension may not offer enough resistance to this pressure. If this occurs in a knot in which the original loop has been tied with a left hand throw, one can readily understand how the knot may slip from the flat condition (fig. 3). The slipping is more apt to happen when the suspended loop of this particular knotted suture is so placed in the tissues that its horizontal axis is subjected to clockwise rotation. Likewise, counterclockwise axial rotation of the loop in a suture knotted by a right hand throw causes it to slip from the flat state.

Fig. 3.—A left hand square knot, showing how the suspended loop in this type of knot can slip from the flat state. If tension or pull on the suspended loop is directed to the right, the knot easily slips from the flat condition. This is especially true of the left hand square knot because the absorption of moisture in the strand causes a counterclockwise rotation of the strand which, in turn, aids the rotation of this particular suspended loop.

Fig. 4.—The austral, *A*, and boreal, *B*, rotation of a square knot on its suspended loop. Note in *B* the loss of twist to the right of the knot and the increase of twist to the left of the knot. In *A* there is an opposite effect on the twist in the material adjacent to the knot. This may be a partial explanation of the earlier dissolution of this particular portion of the ligature or suture; the loss of twist causes early absorption.

In this instance the strand retains its twist providing the knot remains tied, thus preventing rapid absorption in the area adjacent to the knot.

Even when the suspended loop of an interrupted suture is held in a fixed position, vertical rotations of its knot may take place. If they do, variations of strand torsion in the areas adjacent to the knot occur, regardless of the form of the knot. Boreal rotation of a right hand knot causes loss of torsion to the right of the knot and simultaneously produces an increase of torsion to the left of the knot. The reverse is true of the austral rotation of this knot (fig. 4). In the left hand knot,

boreal rotation causes a loss of twist to the right of the knot and an increase to the left of the knot. Austral rotation causes the reverse effects. These factors have a definite effect on the ultimate absorption of the strands in these particular areas.

COMMENT

Particular attention to the physical details mentioned in this paper will give better results in the use of continuous or interrupted catgut sutures. A continuous suture applied in the counterclockwise direction causes a loss of torsion, thereby imparting weakness to the strand. The interrupted suture will be discussed more fully in a future report.

SUMMARY AND CONCLUSIONS

Evidence to demonstrate the relation of torsional variations to tensile strength of knots in the conventionally spun nonboilable (hydrous) catgut suture material is presented. Right hand throws increase the twist in knot tying. Left hand throws decrease the twist. Single knots formed by right hand throws resist less tension than left hand knots when tissues of small diameters are tied, especially when smaller suture materials are used. Knots made by right hand throws resist more tension than those made by left throws when they are tied over tissues of larger diameters.

A knot made by a right hand throw may be tied more easily and more tightly if the clockwise torsion is increased during the act of tying the knot. If the twist is decreased during this procedure, it is more difficult to tie the knot and less tension is obtained within the suspended suture or ligature loop.

In this tying of a left throw knot it is easier to make the knot tight if the torsion of the strand is decreased. (This is not to be recommended as a routine procedure.) If the twist is increased when a left throw knot is being tied, it is more difficult to tie the knot securely.

The loss of twist in catgut suture material exposes more surfaces of the substance to the effect of the tissue juices; this in turn hastens the absorption processes.

Tensile strength on straight pull tests is not the all-important matter. The material should be introduced into the wound in such a manner that the twist is preserved. This applies particularly to the tying of knots whatever their form may be.

There are two forms of square, or reef, knots. The right hand square knot originates with a throw made to the right, or in the same direction as that of the strand twist. The first throw in the left hand square knot is to the left, counterclockwise, opposite to the direction of the strand torsion.

The right hand square knot is the better knot to use in catgut sutures or ligatures for the following reasons: (1) The first, and most important, loop is tied with less tension and injury to the strand; (2) the knot is less apt to slip while the second throw is being tied, and (3) there is increased resistance in its suspended loop to the pressure caused by the absorption of moisture from the tissues, and therefore it is more likely to hold the flat state and preserve the twist in the areas adjacent to the knot.

SPONTANEOUS PNEUMOTHORAX FOLLOWING POSITIVE PRESSURE INTRATRACHEAL ANESTHESIA

REPORT OF A CASE

A. F. HEIDRICK, M.D.

W. E. ADAMS, M.D.

AND

H. M. LIVINGSTONE, M.D.

CHICAGO

Since the introduction of intratracheal anesthesia by Elsberg in 1909, this method of administration has become increasingly popular, especially in the field of thoracic surgery. Elsberg[1] mentioned the difficulties in determining the size of the catheter to be used in order to produce the desired distention of the lung. The determining factor is the freedom of outflow around the catheter. The importance of this is well illustrated in a case recently reported by Bradshaw.[2]

As to the exact amount of positive pressure which may be safely used, there seem to be marked differences in opinion. Coryllos,[3] as a result of his experimental work on human beings and dogs with the E and J resuscitator (using from plus 14 mm. to minus 9 mm. of mercury through the face mask), concluded that it was impossible to cause even the slightest trauma to the lungs with this pressure. He found that if a lung freshly removed from a dog was attached to the resuscitator it expanded and retracted rhythmically and became only moderately distended with a positive pressure of 15 mm. of mercury, and that in order to produce rupture of the lung a positive pressure of from 52 to 58 mm. of mercury was needed.

Macklin,[4] in his study on cats, found that positive intratracheal pressure could produce mediastinal emphysema, pneumothorax and even

From the Department of Surgery of the University of Chicago.

1. Elsberg, C. A.: Clinical Experiences with Intratracheal Insufflation (Meltzer), with Remarks upon the Method for Thoracic Surgery, Ann. Surg. **52**: 23, 1910.

2. Bradshaw, H. H.: Anesthesia for Intrathoracic Operations, J. Thoracic Surg. **8**:293, 1939.

3. Coryllos, P. N.: Mechanical Resuscitation in Advanced Forms of Asphyxia, Surg., Gynec. & Obst. **66**:698, 1938.

4. Macklin, C. C.: Pneumothorax with Massive Collapse from Experimental Local Overinflation of the Lung Substance, Canad. M. A. J. **36**:414, 1937.

subcutaneous emphysema. The time required to produce these changes varied inversely with the pressure used: With relatively small catheters, it was more difficult to produce a pneumothorax.

Eisenbrey [5] showed that there is a wide variation between the pressure registered on the apparatus and that which actually exists in the trachea. In 1 case when there was free outflow of air between the catheter and the trachea, a machine pressure of positive 20 mm. of mercury gave an intratracheal pressure of 1.4 mm.; at 30 mm. of mercury the intratracheal pressure remained the same, and at 50 mm. of machine pressure the intratracheal pressure was 2.2 mm. Quite different were his results when the space between the catheter and the trachea was diminished. With a machine pressure of 20 mm. of mercury and an intratracheal pressure of 1 mm., slight constriction to the outflow raised the machine pressure to 24 mm. of mercury and the intratracheal pressure to 5 mm. Further constriction caused the pressures to rise to 30 and 14 mm. of mercury respectively. Eisenbrey further stressed the rapidity with which the intratracheal and pulmonary pressures rise to a dangerous degree with only a momentary stoppage of the outflow. These facts have been substantiated more recently by Marcotte, Phillips and Adams [6] in studies of dogs and cats.

Bradshaw reported a case of an 18 month old child who was to be operated on for a large intrathoracic neurofibroma. Shortly after the intratracheal anesthesia was begun, subcutaneous emphysema of the neck was noticed, and an associated small pneumothorax on the right side was also present. Uneventful mask anesthesia was given at a later date, and the operation was successfully performed. With the second anesthesia a water valve to prevent too high an intratracheal pressure was introduced into the system. Bradshaw's report suggests that the emphysema and pneumothorax were due to an inadequate outflow of gas around the intratracheal tube. He mentioned the mechanical difficulties in administering intratracheal anesthesia to children, for a tube permitting the use of proper suction and an adequate administration of the anesthetic agent practically fills the trachea.

In 1936, Stephens [7] reported 3 cases of contralateral pneumothorax complicating intrathoracic surgical treatment. In his first case emphysema of the face and chest wall developed five hours after the operation. Autopsy revealed complete collapse of both lungs as well as

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5. Eisenbrey, A. B.: Observations on the Use of Intratrachial Anesthesia in Experimental Work, Surg., Gynec. & Obst. **15**:715, 1912.

6. Marcotte, R. J.; Phillips, F. J.; Adams, W. E., and Livingstone, H.: Differential Intrabronchial Pressures and Mediastinal Emphysema, J. Thoracic Surg. **9**:346, 1940.

7. Stephens, H. B.: A Consideration of Contralateral Pneumothorax as a Complication of Intrathoracic Operations, J. Thoracic Surg. **5**:471, 1936.

a mediastinal emphysema. No actual tear in the mediastinal pleura or bronchial fistula could be found. No mention was made of the method by which the anesthetic agent was administered. In the second case positive pressure through the mask was used. No cutaneous emphysema existed, but autopsy showed contralateral pneumothorax. Again no tear in the mediastinum could be demonstrated. In his third case, the intratracheal tube was in place but the anesthetic mixture was given through the mask. During the operation the heart action ceased. Forced positive pressure was used for the remainder of the operation. The patient recovered after the obliteration of a spontaneous contralateral pneumothorax.

We wish to report a case of spontaneous pneumothorax following positive pressure intratracheal anesthesia administered during an operation on the stellate ganglion.

REPORT OF CASE

B. N., a 19 year old woman, was admitted to the hospital on June 14, 1938, because of pain in the third finger of the right hand following an orthopedic operation in March 1937. At the age of 4 years the patient had a right hemiparesis and aphasia which developed suddenly a few days after a tonsillectomy. The right facial weakness and aphasia gradually disappeared, but severe paresis of the right arm and moderate paresis of the right leg persisted. In 1936 and 1937 she had a series of operations on the right forearm. After the operation in March 1937 she had continuous pain in the right middle finger which was exacerbated by moving the second, third or fourth finger.

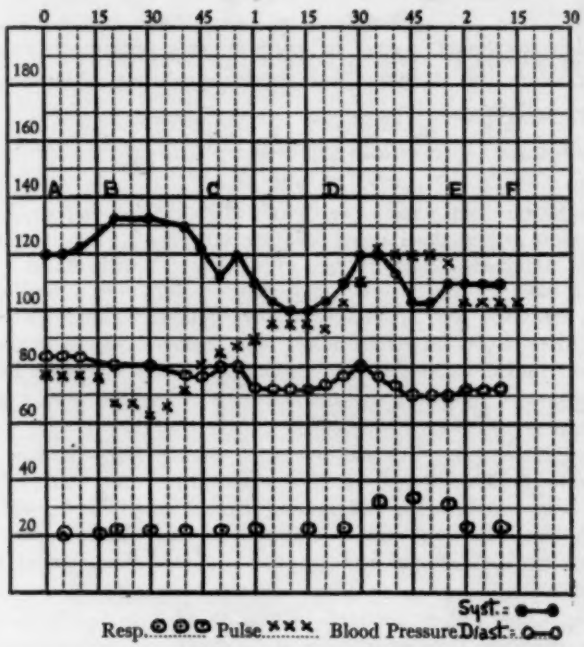
Physical Examination.—The patient was a slightly obese woman of 19 years. General examination revealed a condition essentially normal except for the right arm. This arm was atrophic and spastic, carried in a flexed position with the hand held in the same straight line (owing to a previous bone graft operation), and the fingers were firmly flexed into the palm. There was marked resistance to passive movement.

Treatment.—The patient received infiltration of procaine hydrochloride into the hand, injection into the median nerve at the elbow and paravertebral injection in the right upper thoracic region on different occasions. All of these injections relieved the pain in the finger for a short time.

Operation.—On June 21 a preganglionic sympathectomy (right side) in the upper part of the thoracic region was done. The anesthesia was produced by intratracheal administration of ether and oxygen after an ethylene-oxygen induction. A no. 8 Magill tube was introduced through the nose and directed into the larynx under direct vision. Intubation was easily accomplished, with no evidence of injury to the respiratory tract. There was no mucus in the throat. A no. 16 Foregger bag with an exhalation valve was attached to the intratracheal tube by a 24 inch small rubber tubing. Ether vapor and oxygen were delivered into this bag. Anesthesia was maintained by the semiopen method with the exhaling valve partly open. Some manual pressure was used on the bag during the operation when a hole was made in the pleura, and at a positive pressure of 12 mm. of mercury (as measured at the head of the machine) oxygen was given for three minutes by

attaching the bag to the anesthetic machine just before closure of the chest to secure lung expansion. The exhaling valve remained half open during this time; the right lung was seen to expand well. Throughout the entire operation blood pressure, pulse and respiration showed no marked variations, as is shown in the accompanying chart.

Postoperative Course.—The patient complained of difficulty in breathing as soon as she regained consciousness, but she did not at that time appear dyspneic, and her general condition was good. At 3 a. m. the following day (fourteen hours postoperatively) marked subcutaneous emphysema was noted over the right side of the head and neck, extending below the scapula and over the right temple. The patient was definitely dyspneic. A roentgenogram taken at that time showed a total



Data on the operation which was followed by spontaneous pneumothorax. The abbreviations represent: *A*, beginning of anesthesia; *B*, intratracheal intubation; *C*, beginning of operation; *D*, small hole in pleura, positive pressure; *E*, beginning of closure, positive pressure; *F*, completion of operation.

pneumothorax with complete collapse of the left lung, but no shift of the mediastinum. Four hundred cubic centimeters of air was withdrawn from the left pleural cavity, which resulted in relief of the dyspnea. The next day air was again aspirated at intervals from the left pleural cavity, and the symptoms were again relieved. On the second postoperative day (June 23) the emphysema was less marked, and there was no difficulty in breathing. The subsequent convalescence was uneventful. There was little febrile reaction. On June 28 roentgenograms of the chest were normal. On July 1 the patient was discharged to the outpatient and the physical therapy departments for further treatment of her much improved hand and arm, which were painless after the operation.

SUMMARY

It has been demonstrated both experimentally and clinically that excessive positive pressure used in producing anesthesia may result in serious pulmonary complications. The exact amount of positive pressure which can be safely used is not certain. That the machine pressure is no accurate index of the intratracheal and intrapulmonary pressure was shown experimentally by Eisenbrey in 1912 and more recently by Marcotte, Phillips and Adams. The freedom of outflow around the intratracheal catheter seems to be one of the most important factors in the determination of the amount of positive pressure existing in the tracheobronchial air passages. Bradshaw reported a case in which emphysema and pneumothorax complicated intratracheal anesthesia when no operation was performed. Stephens reported a case of generalized emphysema and contralateral pneumothorax occurring after an intrathoracic operation. No mention was made by Stephens of the type of anesthesia used.

One neurosurgical case in which the intratracheal anesthesia was seemingly uneventful but in which spontaneous contralateral pneumothorax developed postoperatively is reported. In this case relatively low positive pressure was used.

PROBLEM OF CARCINOMA OF THE BREAST

RADICAL MASTECTOMY IN NINETY CASES

C. A. KUNATH, M.D.
SAN ANGELO, TEXAS

The following report represents a study of the patients with malignant tumor of the breast admitted to the University of Iowa Hospitals during a five year period (1927 to 1932), with an analysis of the results five to ten years after radical mastectomy. In this respect it is essentially another report of so-called five and ten year cures; however, it is my endeavor to present a somewhat broader aspect of the subject. Although the percentage of operative "cures" of carcinoma of the breast has been steadily increasing during recent years, there are still certain features which indicate that a final solution to the problem has not been reached. It is hoped to emphasize certain factors which may be of assistance in improving the results.

The better known clinics throughout the United States are now reporting five year "cures" in from 30 to 60 per cent of their cases, and the general tone of the various reports tends to give rise to a feeling of optimism. Some would explain this progress on the basis of improvements in operative technic; others, on the basis of recent advances in the technic of irradiation. A third explanation is that patients are now being seen earlier in the course of the disease and therefore respond more favorably to surgical treatment. Encouraging as these figures may be, one must not lose sight of the fact that they are based only on operable tumors and that they leave untold the fate of a vast number of patients whose lesions are inoperable when first seen by the surgeon and are therefore largely responsible for the high death rate from the disease.

Of the patients studied in the present series, 38 per cent were considered inoperable when first seen. The follow-up study of the surgically treated patients showed five year survivals in 50.5 per cent of instances, a figure which compares favorably with those from other, similar clinics. But when one considers the number of survivals in respect to the total number of patients seen, both operable and inoperable, the percentage of five year survivals drops to about 30 per cent. This is the figure that has real significance when one considers the disease in its entire scope.

In 1927, Daland [1] published the results of a study of 100 untreated patients with mammary carcinoma who had either refused operation or

From the Department of Surgery, University Hospitals, Iowa City.

1. Daland, E. M.: Untreated Cancer of the Breast, Surg., Gynec. & Obst. **44**:264, 1927.

presented evidence of inoperability when first seen. The average duration of life for these patients from the time of the first symptoms was forty and five-tenths months. Twenty-six per cent of the group lived five years without any treatment; 5 per cent lived ten years. Two of the patients lived thirteen years. From the reports of other workers who have followed untreated patients it would appear that the average life expectancy from the first symptoms of carcinoma of the breast is in the neighborhood of three years. With these facts in mind, it becomes evident that the significance of postoperative "five year cures" may be less than has been considered.

Finally, I have shared a growing conviction that the term "cure" is not a good one to use in speaking of patients recovering from radical mastectomy for cancer of the breast. There are numerous instances in the literature of metastases appearing fifteen and twenty years after

TABLE 1.—*Classification of Patients with Mammary Carcinoma*

Operable		91
Radical mastectomy done	90	
Operation refused	1	
Inoperable on admission		56
Treated by irradiation only	41	
Treated by simple mastectomy	15	
Primarily treated elsewhere, entered with metastases or recurrence		18
Carcinoma of male breast*		3
		168

* Carcinoma of the male breast presents a somewhat different problem, and these 3 cases are therefore included in a separate report (Carcinoma of the Male Breast, J. Iowa M. Soc. **28**: 10, 1938).

operation, and 1 case has been reported in which an interval of forty-three years occurred between radical mastectomy and the appearance of metastases. Carcinoma of the breast is notorious in this respect, and there is probably no time in the patient's postoperative life when she may consider herself absolutely free of the possibility of metastases. It would appear, therefore, that the term "survival" is much more appropriate than "cure" in referring to patients who remain in good health for a number of years after operation, and this term will be used henceforth in this report.

During the five year period between July 1, 1927 and July 1, 1932, there were 168 patients with carcinoma of the breast admitted to the University of Iowa Hospitals. These patients are classified in table 1.

The criteria of operability in this clinic correspond closely to those used elsewhere. Radical mastectomy was not carried out when the following conditions presented themselves:

1. Demonstrable metastases to the skeletal system or other remote organs

2. Demonstrable involvement of the supraclavicular lymph nodes
3. Far advanced ulcerative conditions or marked fixation to the chest wall
4. Very poor general condition or associated lesions making the prognosis for life limited
5. Rapidly growing so-called "acute carcinoma" arising in the lactating breast or during pregnancy

Table 2 shows the operability rate as recorded by years. This analysis was also carried through a subsequent five year period (from 1932 to 1937) in order to note any improvement which might have occurred in this phase of the problem. It will be seen that so far as this particular clinic is concerned little progress has been made in regard to the percentage of operable patients reporting for treatment.

TABLE 2.—*Operability Rate*

1927	61.6%	1932	67.9%
1928	50.0%	1933	83.6%
1929	71.4%	1934	56.2%
1930	70.6%	1935	78.0%
1931	68.7%	1936	65.7%

ANALYSIS OF NINETY CONSECUTIVE RADICAL MASTECTOMIES

The cases of the 90 surgically treated patients have been carefully analyzed and present an interesting cross section of the problem of mammary carcinoma in general. The salient features of this analysis are presented in the following sections.

Vital Statistics.—The average age for the group was 52.5 years, the extremes being 74 years and 25 years. There were 17 patients, or 18.8 per cent, under 40 years of age. The time that elapsed between the first symptom of trouble with the breast and the first visit to the physician varied from one day to twenty years. There was usually a delay of from six to eighteen months.

Causation.—There was a history of preceding trauma in only 10 cases, or 11 per cent. Two patients stated that they had had a benign tumor removed from the breast four and five years respectively prior to admission. Ten patients stated that they had had a "caked breast" or an abscess of the breast in the past, again 11 per cent of the entire group. In other words, the majority of patients gave nothing in their history to suggest a possible cause, and this corresponds rather closely with the observation of most other workers on the subject. On the other hand, some observers believe that lymph stasis is a most important factor

in the development of malignant tumor of the breast. Trout [2] was able by careful questioning to elicit a history of some type of dysfunction of the breast in 88 per cent of cases.

Symptoms.—The first symptom noted was usually a mass in the breast, discovered by the patient; this occurred in 84.4 per cent of cases. Pain was the symptom next in frequency, being the first symptom in about 8 per cent of the series. Most of the standard textbooks have minimized the incidence of pain in carcinoma of the breast, stating that the lesion is essentially painless. This is probably true in the early stages, but 39 per cent of the patients in our series were found to have had either pain or tenderness at sometime during the course of the disease. Discharge from the nipple was noted in only 12 cases, or 13.3 per cent. The bloody discharge mentioned in textbook descriptions was noted only 4 times. In 1 case the first symptom discovered was

TABLE 3.—*Distribution of Lesions*

Upper half		61
Upper lateral quadrant	41	
Upper medial quadrant	12	
Both upper quadrants	8	
Lower half		20
Lower lateral quadrant	9	
Lower medial quadrant	6	
Both lower quadrants	5	
Lateral half		51
Medial half		20
Directly beneath nipple		1
Entire breast		1
Axillary tail		1

retraction of a nipple. In another case the first complaint was of neuritic pain down the arm.

Physical Findings.—Many authors have observed that carcinoma of the breast is most frequently located in the upper and lateral quadrants of the breast, and this has proved to be an interesting subject for speculation. In the present series of cases the lesions were located as shown in table 3. It will be seen that there were three times as many tumors in the upper lateral quadrant as in its nearest competitor, the upper medial quadrant. There were 61 lesions in the upper half of the breast as compared to 20 in the lower half, nearly three times as many. There were nearly three times as many lesions in the lateral half of the breast as in the medial half. The usual explanation of this overwhelming preponderance of tumors in the upper half of the breast is that lymphatic drainage is poor because of inadequate support of the breast. The data that have been accumulated are so consistent that there would seem to

2. Trout, H. H.: Carcinoma of the Breast: A Study in Etiology and Prognosis, Am. J. Surg. **24**:258, 1934.

be ample grounds for advising some type of uplift brassiere for proper support of the breast.

Fixation to the skin, including the nipple, was noted clinically in 48 of the 90 cases and served to emphasize again that the familiar orange peel appearance of the skin is a frequent and early finding. Some degree of ulceration of the skin was present in 7 cases.

Axillary Metastases.—The presence of axillary metastases, although not considered a sign of inoperability, is of first importance from the standpoint of prognosis. In this series of radical mastectomies microscopic examination revealed the presence of metastases to the axillary lymph nodes in 55.5 per cent of cases.

Overholt and Eckerson [3] have pointed out that the clinical diagnosis of axillary metastases is often incorrect, since, on the one hand, the nodes may be inaccessible to the palpating finger and, on the other hand, a certain part of the enlargement of the lymph nodes may be on the basis of simple chronic hyperplastic lymphadenitis. Investigation of this point in the present series showed numerous errors in both directions. There were 41 cases in which a clinical diagnosis of axillary metastases was made. In only 30 of these were metastases demonstrated on histologic section, an error of 27 per cent. There were 49 cases in which no nodes were palpated clinically. In 20 of these metastases were demonstrable on histologic section, an error of 41 per cent. Thus, the total diagnostic error was found to be 34 per cent.

Similarly, it was found that the clinical diagnosis of involvement of the skin was often in error. Of the 48 cases in which there was clinical involvement of the overlying skin, sections showed actual invasion of the skin in only 19, or 40 per cent. In the other cases the cutaneous condition was probably simple lymphedema or was due to traction on the skin from deeper structures.

Operative Technic.—The extent of the dissection in radical mastectomy has become pretty well standardized since Halsted described his technic in 1888, and the chief differences of opinion today center around such details as the amount of skin to be removed, the type of suture material to use and the closure of the defect by primary skin approximation or by Thiersch graft. In the present series of cases an attempt was made to preserve skin wherever feasible and to approximate the edges of the skin primarily in every case if possible. As a result, primary skin graft was carried out only 11 times, an incidence of 12.2 per cent.

Postoperative Mortality and Morbidity.—In this group of 90 consecutive radical mastectomies there was not a single operative death. The earliest recorded death occurred three months after operation and more than two months after the patient's discharge from the hospital.

3. Overholt, R. H., and Eckerson, E. B.: The Treatment of Cancer of the Breast and the Results of Operation, New England J. Med. **211**:703, 1934.

Among the postoperative complications, infection led the list, and there were 27 patients, or 30 per cent, who had some degree of sloughing of the cutaneous margins or infection in their wounds. Nine of these defects were considered extensive enough to require secondary skin grafting. The next most common postoperative complication was lymphedema of the arm, which occurred in 10 per cent of the cases. Thrombophlebitis of the axillary vein occurred in 2 cases. There were 1 instance of pulmonary infarct and 1 case in which the postoperative course was complicated by erysipelas of the wound. The average period of hospitalization was twenty-two days, the extremes being six days and ninety-two days.

TABLE 4.—*Status of Patients Five to Ten Years After Operation*

Patients living		32
Living and in good health	31	
Living with local recurrence	0	
Living with metastases	1	
Patients dead		58
Died of carcinoma of breast	52	
Died of other causes*	6	
		90

* Cancer of stomach, 2; cancer of cervix, 1; diabetes, 1; cerebral hemorrhage, 1; psoriasis and general debility, 1.

TABLE 5.—*Percentage of Survivals for Each Year After Operation*

1 year survivals (82 out of a possible 90)	91.0%
2 year survivals (68 out of a possible 90)	75.5%
3 year survivals (59 out of a possible 89)	66.3%
4 year survivals (50 out of a possible 87)	57.5%
5 year survivals (43 out of a possible 85)	50.5%
6 year survivals (32 out of a possible 77)	41.6%
7 year survivals (17 out of a possible 58)	29.3%
8 year survivals (11 out of a possible 40)	27.5%
9 year survivals (4 out of a possible 17)	23.5%
10 year survivals (2 out of a possible 7)	28.6%

FOLLOW-UP RESULTS

I was especially fortunate in obtaining a follow-up report in 100 per cent of cases in this series. The lapse of time since operation varied from five to ten years. The status of the group at the time the survey was made is shown in table 4.

Table 5 shows the percentage of survivals for each year following operation. The term "survival" is used only for patients in good health without evidence of metastases or recurrence.

The incidence of local recurrence in the series was 18.9 per cent. The time of appearance varied from four months to five years postoperatively, the average interval being eighteen and three-tenths months.

The group was not particularly suited for the study of metastases, since most of the patients died at home, and postmortem examinations were not made. However, from the evidence at hand, the following incidence of metastatic lesions was ascertained: skeletal system, 18 (spine, 8; pelvis, 7; ribs, 3; femur, 3; skull, 2; clavicle, 1; sternum, 1); lungs and pleura, 16; liver, 8; peritoneum, 4; opposite breast, 4; mediastinal lymph nodes, 3; skin, 2, and brain, scalp, pancreas, adrenals, larynx and pericardium, 1 each.

Warren [4] in a study of 162 cases of cancer of the breast in which autopsy was done observed only 8 in which there were no metastatic lesions. He stated that practically every organ in the body has been noted as a site of metastases, and in his study the eye, the middle ear, the nasopharynx and the pineal gland were the only tissues to be spared.

COMMENT ON RESULTS

It will be noted from table 5 that the percentage of five year survivals was 50.5, a figure which compares favorably with those reported from similar clinics. Hutchinson [5] in an extensive analysis of the world literature in 1936 found that five year survivals averaged 28.1 per cent with operation alone and 40.9 per cent with operation plus irradiation.

The death rate was highest in the first few years after operation and tended to level off after the seventh year. In other words, for every year the patient survives after operation the prognosis for cure becomes better.

The incidence of local recurrences (18.9 per cent) may seem unduly high and caused my associates and me to consider the advisability of wider cutaneous excision. After Halsted devised his "complete" operation in 1888, he reported that he had reduced the incidence of local recurrence from over 60 per cent to 6 per cent.[6] However, at that time the longest postoperative duration of life in any of his patients was about three years. Subsequent reports by Halsted put the figure at 9 per cent, then 27.1 per cent, then 31.9 per cent. Lewis and Rienhoff,[7] in an analysis of the cases from the Johns Hopkins Hospital in 1932, reported local recurrences in a range from 32.2 to 15.2 per cent of cases. These authors made a strong plea for wide cutaneous excision and

4. Warren, S., and Witham, E. M.: Studies on Tumor Metastases: The Distribution of Metastases in Cancer of the Breast, Surg., Gynec. & Obst. **57**:81, 1933.

5. Hutchinson, R. G.: The Value of Radiation Therapy in the Treatment of Carcinoma of the Breast, Surg., Gynec. & Obst. **62**:653, 1936.

6. Halsted, W. S.: Surgical Papers of William Stewart Halsted, Baltimore, Johns Hopkins Press, 1924, vol. 2.

7. Lewis, D.; and Rienhoff, W. F.: A Study of the Results of Operations for the Cure of Cancer of the Breast, Ann. Surg. **95**:336, 1932.

primary Thiersch graft, stating that by this procedure alone is it possible to reduce local recurrences to a minimum.

Although these views reflect the teaching of Halsted, who may properly be called the father of modern breast surgery, there are enough accumulated statistics to lend considerable doubt as to their practicability. In the first place, the percentage of recurrences reported by these authors is not as low as those of some clinics where closure of the wound is carried out primarily. Lee [8] in analyzing the cases from the Memorial Hospital, New York, found local recurrences in only 13 per cent, and nearly all of the operative wounds were closed primarily without grafting. In the present series of cases primary skin grafting was carried out eleven times owing to extensive ulceration necessitating wide excision of skin. It is probably true that these patients represent a group in a more advanced stage of the disease and therefore a less favorable prognosis. Be this as it may, the fact remains that there were local recurrences in 47.3 per cent of this group as compared to 17.7 per cent in which primary closure was done.

Secondly, the postoperative mortality is appreciably higher where the Halsted Thiersch graft procedure is employed, and in the series reported by Lewis and Reinhoff it was 6.4 per cent.

Finally, one must face the fact that the patient with carcinoma of the breast does not die from local recurrence but from metastases, and often these are far distant from the site of the primary lesion.

It is the opinion of this clinic, therefore, that a point has been reached where one can expect little improvement in results from increasing the magnitude of the operation. This viewpoint has been admirably expressed by Mathews,[9] who stated: "We may extend the area of skin removal indefinitely but what is gained when the site of the recurrence is within the chest?"

FACTORS IN PROGNOSIS

A great deal of insight into the problem of carcinoma of the breast can be gained by consideration of the various factors influencing prognosis. The factors which have been mentioned in the past are discussed briefly in connection with the present series of cases.

1. *Age.*—The influence of age is well known and follows the generally accepted fact that any malignant growth occurring in a young person is apt to be much more rapidly growing and earlier to metastasize. In the present series of 90 cases there were 17 patients under 40 years of age, with five years survivals in only 5 instances, or 29 per cent.

8. Lee, B. J.: End Results in the Treatment of Cancer of the Breast by Radical Surgery Combined with Preoperative and Postoperative Irradiation, Am. J. Surg. **20**:405, 1933.

9. Mathews, F. S.: Results of Operative Treatment of Cancer of the Breast, Ann. Surg. **96**:871, 1932.

2. *Lactation.*—Although there has never been any conclusive proof that cancer occurs more frequently in breasts which have lactated, some workers believe that there has been some type of dysfunction in the breast in practically every case of malignant disease. On the other hand, it is rather definitely established that carcinoma arising in an actively lactating breast or during pregnancy is an exceedingly dangerous lesion. Five year survivals in such cases are practically nonexistent. Trout [10] warned women never to become pregnant after having had an operation for cancer of the breast. Of 15 collected cases in which postoperative pregnancy occurred, cancer developed in the opposite breast in 13, or 87 per cent, and all 13 patients died promptly of carcinoma. Although there are no such cases in the present series, I have observed several during the past few years and have learned to consider such lesions as among the most rapidly growing and progressively fatal of all malignant growths. The practice of producing artificial menopause in the treatment of malignant mammary disease is becoming generally adopted throughout the United States and is logically based on the known inter-relation between the breast and the ovaries. The factor of lactation in prognosis can probably be summed up by saying that if it is coexistent with a malignant tumor of the breast the prognosis is made much more unfavorable, while previous lactations exert a detrimental effect only so far as they have left residual dysfunction, irregularity or inflammatory episodes.

3. *Duration of Symptoms Before Operation.*—For evaluation of the importance of this factor, see section 4.

4. *Rate of Growth.*—Greenough and Taylor [11] stated that the preoperative duration of the tumor, as recorded by the patient, is of very little value in prognosis. Lewis and Rienhoff [7] also found this factor to have very little significance in regard to longevity after operation. My own observations are in agreement with these views, and in the present series some of the patients who had delayed longest before consulting a physician are among those who have survived for five years. Since there is such a great variation in the rate of growth of carcinoma of the breast it would appear that this factor is the important one to consider, rather than the actual time that the tumor has been present. One can probably conclude, therefore, that while the duration of symptoms is of minor importance, the rate of growth is probably among the most important of prognostic factors.

5. *Size of Mass.*—An analysis of this point failed to reveal that a large tumor carries any more serious a prognosis than does a small one.

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10. Trout, H. H.: Carcinoma of the Breast, Surg., Gynec. & Obst. **60**:476, 1935.

11. Greenough, R. B., and Taylor, G. W.: Cancer of the Breast: End Results, New England J. Med. **210**:831, 1934.

Here again the significant feature is not the size of the mass but the rate of growth and the extent of the disease at the time of operation.

6. *Location of Mass.*—Lee [8] has stated that tumors of the upper medial quadrant of the breast carry the best prognosis, while those of the lower half and upper central position carry the most unfavorable. I was unable to verify this conclusion in the present series of cases and found the percentage of five year survivals to be practically the same for each quadrant of the breast examined.

7. *Axillary Metastases.*—The importance of axillary metastases in prognosis is probably the best accepted of any of the various factors that have been discussed. This point has been analyzed by practically all workers on the subject, and the conclusions are quite consistent throughout. Hutchinson,[5] in his review of the published statistics in 1936, found the average percentage of five year survivals to be 35 in cases in which there were axillary metastases and 71.3 per cent in cases in which no axillary metastases were present—a difference of 36.3 per cent. An analysis of the present series of cases shows figures which are very similar:

Total 90 cases	50.5% five year survivals
40 cases without axillary metastases	72.5% five year survivals
50 cases with axillary metastases	30.0% five year survivals
Difference	42.5%

An analysis of the cases in which death occurred showed that the average duration of life in the patients with axillary metastases was two and sixty-seven hundredths years, while those without axillary metastases lived an average of four and seventeen hundredths years, or nearly twice as long.

Doubtless, if it were possible to subdivide the patients with axillary metastases still further—as to the portion of the axilla involved, size of the nodes, and degree of fixation—one could gain even greater prognostic information. Trout [10] has mentioned that one large axillary node gives a much better prognosis than do numerous shotlike glands, and it has been common observation that when the extremely apical glands of the axilla are involved the prognosis is made definitely less favorable. In the experience of Bloodgood [12] the five year survivals will average about 70 per cent when the axillary glands are not involved. When these glands are involved the figure drops to 25, 20 and 10 per cent, depending on whether the basal, the medial or the apical glands are involved and on the skill of the operator.

8. *Involvement of Skin.*—This feature was analyzed without finding anything of prognostic significance. The patients with involvement of the

12. Bloodgood, J. C.: Biopsy in Breast Lesions, Ann. Surg. **102**:239, 1935.

skin lived just as long as the others, and there were 57.9 per cent of five year survivals in this group as compared to 50.5 per cent for the entire series.

9. *Histologic Grading.*—Numerical grading was not carried out in this series of malignant tumors, but some workers feel that this procedure is probably the best index of prognosis that has been discovered. The modified Broder's classification developed by Greenough [13] at the Massachusetts General Hospital proved to be a valuable prognostic index in his hands; nevertheless, he stated the belief that it should always be considered in connection with the extent of the disease and other factors. Lewis and Rienhoff also expressed doubt whether prognosis should be based on the histologic picture alone. Trout [10] stated that the histologic index is not nearly as important or as accurate as a well considered clinical index.

Among the various clinical indexes which have been formulated, probably the most popular is that of Lee and Stubenbord.[14] These authors have taken into account four factors: age, lactation, rate of growth and extent of the disease, which, as may be recalled, are the most significant of the several factors which have just been discussed. Each of these factors is evaluated as increasingly significant in the order named, and they are further evaluated by gradation factors within themselves. Although clinical application of the formula may appear somewhat laborious, it serves to emphasize the relative importance of the various factors to be considered in prognosis.

THE PROBLEM FOR THE FUTURE

The importance of any survey of postoperative results lies in the opportunity it affords for looking into the future. What are the ways and means at hand for improving the results? It is already fairly evident that no drastic improvement can be made from the standpoint of operative technic. The various electrical units and the hot loop knife have many advocates and probably offer certain advantages in all surgical procedures on malignant tumors. As concerns the many incisions that have been proposed, it would seem that this is a matter to be individualized for each patient according to the location of the mass in the breast and the extent of involvement. There is probably no one incision that can be used successfully in every case, and the extent of the subsequent dissection varies little with any of those proposed. The views of this clinic in regard to extensive excision of skin and primary skin grafting

13. Greenough, R. B.: Five Year Cures of Cancer of the Breast at the Massachusetts General Hospital, Surg., Gynec. & Obst. **58**:437, 1934.

14. Lee, B. J., and Stubenbord, J. G.: A Clinical Index of Malignancy for Carcinoma of the Breast, Surg., Gynec. & Obst. **47**:812, 1928.

have already been expressed. Our experience has led my associates and me to agree with Mathews that the percentage of cures of carcinoma of the breast is not proportionate to the time devoted to the operation or to the amount of skin removed. The important thing would appear to be a reasonable type of radical mastectomy carried out while the lesion is sitll confined to the breast.

With this objective in mind, at least three avenues of approach to the problem are suggested:

1. Prophylaxis
2. Education of the laity
3. Irradiation

1. *Prophylaxis.*—The relation of cancer of the breast to previous dysfunction has already been mentioned under the discussion of causation. The occurrence of two thirds of all mammary cancers in the upper half of the breast cannot be ignored and argues strongly for proper support of the breasts as an important prophylactic measure. The relation of pelvic disorders, the proper care of the breasts during pregnancy and lactation and the effect of subsequent pregnancies after removal of a carcinoma of the breast have all been admirably brought to light by Trout [10] and deserve the attention of every practicing physician.

2. *Education of the Laity.*—This approach to the subject is based on the firm knowledge that earlier recognition of the disease is the best means at hand of improving the results. It is highly significant that radical mastectomy in this clinic when carried out before the axillary glands were involved offered a five year survival in 72.5 per cent of the cases. The crux of the problem lies in obtaining a reduction in the large number of tumors which are inoperable when first seen by the surgeon. The American Society for the Control of Cancer is already making strides in this field in educating the laity as to the first signs of the disease and the serious implications that may attend any lump in the breast. That this propaganda is actually producing results has already been shown in some clinics if not in this one. At the Mayo Clinic the operability rate rose from 55 per cent in 1926 to 73 per cent in 1936, and other clinics are reporting similar increases.

3. *Irradiation.*—It seems likely that the radiologist will play an even more important role in the future treatment of malignant disease of the breast than he has in the past. Definite advances are constantly being made in this field by the use of higher voltages and by newer methods of application. The principle of preoperative irradiation appears to be gaining favor steadily, in spite of the disagreements about it a few years ago.

In most of the cases reported in the present study radiation was given after mastectomy, but in none of them was preoperative irradiation

carried out, because this procedure was not instituted at the University Hospitals until 1932. Since 1932 it has become a routine procedure, but there has not yet been sufficient time to permit evaluation of the results in terms of five year survivals. Consequently, the experience of this clinic in this regard is still in terms of impressions rather than actual statistics. The reports from other clinics concerning preoperative irradiation are for the most part encouraging, and as advances are being made in the field of roentgen therapy the use of irradiation may become an even more valuable adjunct to surgical treatment than it is at present.

SUMMARY

Another series of operative cases of carcinoma of the breast is added to the literature for the statistical value it may afford. This report represents an analysis of the results from five to ten years after radical mastectomy, a follow-up report having been obtained in 100 per cent of the cases.

The various factors in prognosis are discussed in regard to their relative importance, the most significant ones being the presence or absence of axillary metastases, the rate of growth, the coexistence of pregnancy or lactation and the age of the patient.

It is suggested that the term "survival" be substituted for "cure" in referring to patients who live for varying periods after operative treatment.

An attempt has been made to view the problem of cancer of the breast in its entirety rather than as a survey of a group of operative cases. The methods of improving the results become more clearly defined when viewed from this standpoint and seem to be chiefly along the lines of prophylaxis and earlier recognition of the disease.

The differences of opinion that exist in regard to operative technic are discussed, and the conclusion is reached that no improvement in end results can be hoped for by making the operation more radical. Rather, the goal should be a reasonably radical mastectomy performed while the malignant growth is still confined to the breast.

EFFECTS OF LOCAL REACTION IN SPONTANEOUS TUMORS OF ANIMALS AND HUMAN BEINGS

FREDERICK M. ALLEN, M.D.
NEW YORK

It has been shown elsewhere [1] that temporary asphyxia produced by local ligation damages tumors selectively, in such a manner as to cause extensive and sometimes complete necrosis of the tumor while the normal tissues are unharmed except for transitory inflammation. These results (with transplanted tumors of rats and mice) were substantially duplicated with the chicken sarcoma,[2] which is composed of autogenous cells, but the persistence of the chemical excitant was assumed to be responsible for the trivial number of actual cures in proportion to recurrences and deaths. It was obviously desirable to extend the trials of asphyxia to tumors native to the mammalian body. Circumstances unfortunately did not warrant undertaking the chemical production of tumors with tar derivatives. A number of rat and mouse tumors were obtained by special arrangements with large dealers.

1. RAT FIBROMA

This is a common benign growth which develops slowly to huge size, sometimes being as large as the rat's body. It also springs usually from a rather narrow pedicle or is sufficiently separate from the body to permit ligation. As it is composed essentially of a low order of tissue, namely, tough, mature white fibrous tissue, it might be expected theoretically to survive prolonged asphyxia. Three examples of different sizes were obtained, and all were found to break down with trivial ligations of one or two hours. This result was not due to thrombosis in the rather scanty supply of main blood vessels, as was shown by the finding of liquid blood and small hemorrhages afterward. The process rather begins as an extensive central necrosis which spreads rapidly to the periphery. In the case of large tumors the shock and gangrene kill the rat. The endurance of temporary lack of circulation is therefore vastly less in a fibrous tumor than in normal tissues of a similar order, such as connective tissue or bone.

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1. Allen, F. M.: To be published.

2. Allen, F. M.: Am. J. Surg., to be published; Transfusions and Polycythemia in Normal and Tumor-Bearing Rats, J. Lab. & Clin. Med. **25**:471-475, 1940; Influences of Local Asphyxia, Organ Extracts and Temperature Changes on Engrafted Subcutaneous and Visceral Tumors in Rats, Urol. & Cutan. Rev. **44**: 12-18, 1940.

2. MOUSE TUMORS

Seven mice with large tumors were received. Small biopsy specimens were examined by Dr. A. S. Price, of the Polyclinic Hospital, who furnished the microscopic diagnoses of 1 mammary adenoma, 1 adenoma with early malignant change and 5 carcinomas. Attempts to transplant the tumors into other mice failed. All these tumors showed typical hemorrhagic congestion, and all visible tissue sloughed completely after ligations of only one and one-half to three hours, while the legs or other normal structures included in the ligatures were unharmed. Some of the tumors were so situated that the entire mass could not be surrounded by a tourniquet. Others were so large that their necrosis resulted in the death of the mouse. One cure with survival was obtained. The animal had an inguinal carcinoma measuring 1.5 by 1.2 by 1 cm. The ligature was placed so as to include the tail and the rectal and vaginal openings but not the leg. After release in one and one-half hours there was the usual dark congestion of the tumor and pink hyperemia of the normal parts, followed by rapid sloughing and subsequent healing of the ulcer.

These results, together with the observations on chicken sarcoma, sufficed to prove that native tumors break down under asphyxia in the same manner as do implanted tumors. The ease of such breakdown is independent of the native or foreign origin of the tumor and likewise of the tissue type of malignancy. Thus, the benign rat fibroma succumbs more easily than the transplanted rat sarcoma or carcinoma. The native adenoma or carcinoma of the mouse is fully as sensitive to asphyxia as the transplanted mouse tumors and much more sensitive than the transplanted rat tumors. An analogy may be drawn with the variable radiosensitivity of different human tumors and with the fact that transplanted tumors in general are not more radiosensitive than native tumors.

3. DOG ADENOCARCINOMA

A dog which was to be killed because of tumor was donated to me by a veterinarian, Dr. Frank Bloom of Flushing, L. I. It was a gray Cairn terrier, female, vigorous, slightly obese and not markedly senile. There were two subcutaneous masses, one on each side of the midline of the abdomen, near the costal margin, about the size of an egg and a walnut respectively, about 8 cm. apart and both hard and nodular. The tentative diagnosis of mammary adenocarcinoma was confirmed by a biopsy of material from the larger tumor.

With the dog under pentobarbital sodium anesthesia a clamp was passed deeply beneath the center of the large tumor, through cutaneous punctures about 2 cm. from its margin, carrying two rubber ligatures. This procedure was repeated in a line at right angles to the first. By tying off the four quadrants thus created, all blood supply was cut off from the large tumor. The ligation was maintained

for six hours. In a small animal, such as a rat, the direct pressure of ligatures for this length of time without protection of the skin ordinarily results in obliteration of vessels and sloughing of the entire mass, but the larger and tougher vessels of the dog resist the injury. Just before release, it was discovered that a trifle of blood flow was present in the tumor, and the cause was found in the breaking of one of the strands of rubber. The tumor swelled greatly after release, but its color was not discernible. The inflammatory reaction and edema also extended over a considerable surrounding area and included the tumor on the opposite side. During the following week or two both tumors shrank gradually, until the large one was about half and the smaller one about two thirds of its original bulk.

One month after the first treatment, both tumors were stationary or showed very slight growth. A small biopsy specimen from the larger one resembled the former specimen except for considerable fibrosis. With the dog under pentobarbital sodium anesthesia a pair of rubber ligatures were passed under the center of the tumor through cutaneous punctures about 3 cm. from the margins, and the smaller size now permitted tying off in two halves. Complete stoppage of blood flow was thus maintained for four hours. The resulting inflammatory reaction was followed by a further slight shrinkage of both tumors. The large one in particular became noticeably flabby, in contrast to its original hard angularity. The normal tissues included with the tumor within the ligature in both treatments suffered no permanent damage.

Two weeks after the second treatment the tumors seemed to be stationary but not receding further. A third treatment was then given by ligating the large tumor in two halves for six hours. The result was immediate sloughing of all visible tissue in this tumor. The normal tissues included within the ligature were merely inflamed, with the exception of a small patch of skin over the center of the tumor, which was lost secondarily in the ulceration. The small tumor maintained its reduced size, without perceptible growth or recession.

One month after this third treatment the ulcer was healed down to a tiny superficial area, without sign of recurrence. The dog then escaped from the laboratory, so that the opportunity for treatment of the small tumor and final proof of cure was lost.

The experiment was of particular interest for two reasons; first, the partial recession obtained in the first treatment when the blood flow was not completely stopped; second, the partial recession in the smaller tumor, which was not ligated but was merely involved in the spread of inflammation from the treated tumor. The conditions here seem to resemble those in some cases of recession of human tumors in the literature. These conditions had not been reproduced in any of the tumors of rodents, in spite of the utmost efforts in this direction from the beginning of the research. In rats and mice, ligation either causes immediate sloughing of a tumor or leaves it in active growth. In rats, at least, tests showed inflammation to be ineffectual without asphyxia. It was therefore of great interest to find a suggestion of radical differences in behavior of tumors due to species.

4. HUMAN CANCER

Two cases were studied in an attempt to apply some of the experimental results and also to gain additional information.

REPORT OF CASES

CASE 1.—Mrs. J. D., aged 48 years, was referred to me by Dr. Edward A. Kellogg. In 1929 Dr. Kellogg had removed the left breast for a tumor which was diagnosed microscopically as a scirrhous carcinoma of mammary duct origin. The patient appeared in perfect health until September 1935. Then, after this unusually long latent period of six years, a small cervical swelling appeared. On September 9 glands were removed, which were found microscopically to contain tumor identical with the original one. Another cervical swelling led to removal of another group of glands on October 1, and still others were excised on Jan. 3, 1936, with the same microscopic picture in all. Roentgen treatments were given to the limit of safety without any effect. Increased rapidity of tumor growth was evident. The patient was seen in consultation on March 3 and received experimental treatments at short intervals from that date until her death from intrathoracic metastases on December 14.

On March 3 the left side of the neck showed five healed scars in different areas where glands had been removed. There was a sprinkling of hard superficial glands from shot to bean size over the left side of the neck, from the midline in front to the midline behind. A fused clump of such glands was palpable below the margin of the jaw. The only sign of deep glandular involvement was an almond-sized mass about midway between the jaw and the clavicle and adjacent to the carotid sheath.

It would have been preferred to try ligation of some of the easily accessible glands. The patient positively refused further surgical treatment of any description but was eager to cooperate in any other kind of experiment. Therefore, treatment was directed to attempts to imitate the local conditions of streptococcic infection. Most of the time was occupied with very mild applications of new measures, which were increased gradually enough to assure against harm. With many variations, the main procedures were as follows:

1. Potassium arsenite [3] was used as a nonirritating form of arsenic, and on one occasion arsphenamine was used as an irritating form. The method varied from injection of a few drops of undiluted solution of potassium arsenite U. S. P. into the center of a small gland to infiltration of large volumes of high dilution over large areas. Because of a high individual tolerance or for other reasons, it was possible to raise the dose as high as 1 cc. without signs of intoxication. Procaine hydrochloride or sometimes cocaine hydrochloride was included in the solution, together with epinephrine hydrochloride and sometimes also ephedrine hydrochloride. Stoppage or reduction of circulation was attempted in three general ways:

a. Small injections were repeated every ten or fifteen minutes, so as to keep an individual gland and its immediate environment saturated with the arsenic for four to six hours continuously. The white wheal caused by the vasoconstrictor substances was always evanescent and was replaced by pink in spite of all efforts. Also, the hardness of the gland caused the fluid to escape from it into the loose tissues of the neck.

b. The same solutions were used with the addition of dextrin or acacia to make as thick a mixture as would flow through the needle, so as to favor local pressure and diminish the spread through the tissues and also for the sake of possible prolonged tissue reactions to the colloids.

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3. Allen, F. M.: To be published.

c. On one occasion the solution was diluted to 1,500 cc., and the attempt was made to maintain local anemia by fluid pressure, fresh solution being injected whenever the tension diminished. Pressure sufficient to cause visible bulging of the pharynx on inspection inside the mouth was thus maintained for three hours and somewhat less pressure for two more hours, but the influence for preventing circulation was inadequate.

The breaking down of cancerous glands by methods *a* and *b* was more successful than might have been expected from the imperfect infiltration and anemia. This tumor, however, was highly resistant to arsenic, because it continued a slow, infiltrating growth after the glands were broken down. Method *c* accomplished nothing. It did not cause any breaking down of glands in the infiltrated area, and the subsequent appearance of new nodules proved that it failed in the main purpose for which it was used, namely, the killing of invisible deposits of cancer throughout the lymph spaces.

2. Pure glycerin, saturated solution of sodium chloride and other strong irritants were injected into cancerous glands, alone or with arsenic. These forms of inflammation proved to be unnecessarily painful without any helpful effects in killing cancer.

3. Injections of Coley fluid (a mixture of the toxins of erysipelas and Bacillus prodigiosus [4]) with cocaine or procaine hydrochloride, epinephrine and sometimes arsenic were made at intervals of fifteen to thirty minutes, so as to keep individual glands saturated with the streptococcus toxin (with or without arsenic) for several hours. Sometimes these treatments were repeated over a series of days. Glands were thus broken down, but more or less infiltrating growth continued. With ascending doses of Coley fluid the additional influence of fever was tested, with rectal temperatures up to 103.4 F., but without any striking change in the results.

4. One gland together with its immediate environment was infiltrated with a starch suspension on two days, causing a mild chronic inflammatory reaction. A biopsy specimen was obtained, and Dr. A. S. Price, without knowing what had been done, made a microscopic diagnosis of carcinoma together with "foreign body granulomatous reaction and multinucleated giant cell formation." The tumor growth was not arrested.

Several applications of roentgen rays were made by Dr. A. J. Quimby according to two plans.

a. In view of the reported dangers of the combination of roentgen therapy and some arsenicals,[5] it was desired to learn whether the tumor might be more sensitized than the normal tissues and also what the effect would be when the tissues were directly infiltrated with arsenic in far higher concentration than could result from any systemic administration. From cautious beginnings with minimal doses of both the drug and the rays (over small areas) advances were made gradually to full erythema irradiation and 1 cc. of solution of potassium arsenite U. S. P. A systemic action must also have resulted from absorption of the injected material. Nevertheless, there was no perceptible sensitization of either the tumor or the normal tissues. At least with regard to this single case, it had to be concluded that the fears concerning arsenic in connection with roentgen therapy were unfounded; there was also absence of benefit.

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4. Coley, W. B.: Late Results of the Treatment of Inoperable Sarcoma by the Mixed Toxins of Erysipelas and Bacillus Prodigiosus, Am. J. M. Sc. **131**: 375-430, 1906.

5. Hueper, W. C., and Itami, S.: Effects of Neoarsphenamine on Spontaneous Breast Tumors of Mice, Am. J. Cancer **17**:106-115, 1933.

b. While the first experiments were being performed on the superficial glands, the mass of deep glands grew rapidly to walnut size. On account of their close proximity to the carotid sheath, pressure disturbances could be anticipated, and a problem of treatment was created. A hint was taken from the roentgen treatment of carbuncle. With a long, thin needle this mass was given daily injections of ascending doses of Coley fluid and arsenic. The increasing inflammation quickly produced the equivalent of an aseptic carbuncle, with the typical swelling, redness and induration but with only tenderness instead of severe pain. A single application of roentgen therapy (⅔ erythema dose) was then given, and the entire mass promptly liquefied and discharged through a small opening. During the following six months of observation, no further swelling appeared in this region or anywhere in the deep cervical glands. There were no circulatory or nervous disturbances at any time.

The net result of all the treatments was an absence of distinct tumor masses or any increase of bulk in the affected side of the neck. The tissues were considerably indurated by the repeated inflammations and obviously also by a thin, diffuse growth of tumor. Three small sinuses were left, which discharged a trifle of serous fluid. All pressure symptoms were prevented, and as far as the neck was concerned there was no need for sedatives except briefly, at the time of the most strenuous treatments. In contrast, the intrathoracic growth gradually produced marked edema and pain in the left arm, requiring large doses of morphine toward the end.

Comment.—On the whole, this tumor was characterized by high resistance to arsenic and streptococcus toxin, in addition to the mechanical difficulties of infiltration. The question of its possible response to asphyxia remains unanswered. From this single experience and on general principles, it appears fairly probable that any tumor mass, even of a radioresistant type and in an inoperable location, can be broken down by converting it into an aseptic carbuncle by injections of any suitable inflammatory agents and then administering a moderate dose of roentgen radiation. The slough consists of the tumor and the inflammatory exudate, not the normal tissue, and blood vessels will presumably not be endangered unless there is actual invasion of their walls by tumor. The plan may possibly have some practical application in cases in which the direct pressure of tumor masses is serious. Whether any such local masses can be actually cured by the method is problematic and may depend on the type of the tumor and other special conditions. The conversion of a radioresistant into a radiosensitive tumor appears theoretically interesting.

Case 2.—W. H., aged 76 years, with senility, moderate obesity and myocardial degeneration, came to the dermatologic clinic of the Polyclinic Hospital with an ulcerated cancer of the face which was diagnosed microscopically as a squamous cell carcinoma. The treatment of a reputedly radioresistant tumor in this location presented difficulties. Permission to attempt it was granted by Drs. Frederick H. Dillingham and A. H. Montgomery, in charge of the clinic.

At the time of the patient's admission to the hospital, Oct. 2, 1935, the tumor was a fungating mass 5 by 8 cm., with the appearance and location shown in the accompanying illustration (*A*). On the following day, with the region under

local anesthesia, Dr. Robert E. Brennan placed a temporary ligature on the external carotid artery. Attempts were then made to produce anemia of the tumor by means of special splints, a rubber bandage and air compression. The effort had to be abandoned because of pain too great to be controlled by morphine and unsatisfactory arrest of circulation and also because direct pressure is different from simple anemia and endangers the normal tissues too seriously. The ligature was removed from the artery, and the cervical wound was closed.

On October 6, with the region under local procaine hydrochloride anesthesia, Dr. Brennan made six punctures through the skin about the periphery of the

A, lesion before treatment; *B*, lesion after treatment.

tumor and 1 to 1.5 cm. from its margin. Rubber ligatures were passed through these openings and tied, but they left a little circulation in the tumor from the underlying parts. The ligatures were released after one and one-half hours. There were slight darkening of the tumor and hyperemia of the surrounding tissues. There were also slight facial palsy and slight sloughing of superficial layers of the tumor.

On October 10, Dr. Brennan again inserted rubber ligatures and this time burrowed deeply with a clamp under the center of the tumor, after which the two halves of the tumor were ligated off with several rubber ligatures passed through the previous cutaneous punctures. With the posterior half the ear was also deprived of circulation. Complete asphyxia was thus maintained for three

and one-quarter hours. On release, the tumor immediately showed the deep blue color of typical hemorrhagic congestion, while the normal tissues flushed bright red, making a sharp line of demarcation. During the following days there was an equally sharp sloughing out of the tumor without loss of any normal tissue. The ulcer healed rapidly, and the partial facial paralysis passed off completely within two to three weeks. The result is shown in the illustration (*B*).

The microscopic slides and the patient were seen by staff members at the Memorial Hospital, where it was first pointed out that a nonulcerated induration indicative of an extension of the tumor was forming at the margin of the mandible, strictly outside the line of the former ligatures. The patient was pleased and grateful but positively refused any further surgical treatment for a lump which was giving him no inconvenience. When it reached the size of a large lima bean, he was persuaded to try an injection treatment. This was based on the current doctrine that certain tumors are killed in their deep parts by an arsenic paste applied on the surface, by a selective process which spares the normal tissues. In this event, the killing of the more remote parts of the tumor must be due either to the simple inflammatory reaction or to a specific action of arsenic dissolved in the tissue fluids. Starting from this premise, 0.5 cc. of solution of potassium arsenite U. S. P. was added to 60 cc. of physiologic solution of sodium chloride together with epinephrine hydrochloride and procaine hydrochloride. Small quantities were injected into the tumor approximately every ten minutes until the entire amount was used up (in two hours). The firm tissue here afforded favorable physical conditions, because the white wheal created by each injection lasted an appreciable time, and sufficiently frequent repetitions maintained a state of approximate bloodlessness through the entire period. The infiltration and saturation of the tumor were also satisfactory, without undue spreading of the solution. In contrast to the violent reaction to any caustic paste, the later effect was so trivial as to create the suspicion that nothing had been accomplished. Within a few days, however, the tumor was found to have disappeared. The patient lived, free from tumor, for two years and died of myocardial failure.

Comment.—Two comments in particular are suggested. 1. A tumor in some other location would have been strongly preferable for a first trial of ligation, because there were inevitable misgivings that the ear might slough off. The animal experiments, however, seemed to give sufficient assurance that the normal tissues could endure much more than three hours of asphyxia. This cancer happened to be killed within the same period as a mouse tumor, but other types might require a considerably longer time. The specificity of the effect is strikingly displayed in the destruction of the tumor on the lobe of the ear without any residual defect in the normal tissues of the ear. 2. This tumor was obviously of a feeble type and a low grade of malignancy. Nevertheless, it was of a type known to be more radioresistant than some highly malignant types. It is easily conceivable that this type of tumor, which is killed by a simple injection of arsenic, might happen to be cured by a streptococcic infection, but there are also records of much more formidable tumors which have disappeared or receded markedly under infection. Evidently, therefore, different types of tumor differ irregularly in their susceptibility to various injuries.

GENERAL COMMENT

Cures of inoperable malignant tumors in man are attested by conclusive evidence and accepted by conservative authorities. The complete cures or extreme recessions number into the hundreds and fall into two classes: first, a few cases in which malignant growths have receded extensively or disappeared completely in connection with mild cellular reactions or under unknown conditions,[6] and second, a much larger group in which the recession or disappearance has resulted from severe infections, such as erysipelas (Fehleisen, Coley) or peritonitis, accompanied by extreme fever and intoxication.[7] With the improvements in surgery, which have abolished most of these complications, the cures of inoperable malignant tumor have also ceased. Inasmuch as clinical clues have always furnished the best guidance for advances in knowledge and treatment, it is important to emphasize the cures or remarkable recessions that have occurred in cases of extensive glandular involvement and of pelvic cancer with visible metastases scattered over wide peritoneal areas. Apart from the spontaneous recessions, the salient therapeutic point is found in the numerous assertions that the drastic use of heat in particular and to a less extent of caustics and other agencies [8] may be followed by death of deep tumor cells which have not

6. Rubens-Duval, H.: Considérations sur les réactions de l'organisme à l'égard du cancer et la thérapeutique anticancéreuse, Progrès méd., 1931, pp. 609-619. Hodenpyl, E.: Treatment of Carcinoma with the Body Fluids of a Recovered Case, M. Rec. **77**:359-360, 1910. Handley, W. S.: The Natural Cure of Cancer, Brit. M. J. **1**:582-589, 1909. Mackay, C. G.: A Case That Seems to Suggest a Clue to the Possible Solution of the Cancer Problem, ibid. **2**:138-140, 1907.

7. Rohdenburg, G. L.: Fluctuations in the Growth Energy of Malignant Tumors in Man, with Especial Reference to Spontaneous Recession, J. Cancer Research **3**:193-225, 1918. DeCourcy, J. L.: Spontaneous Regression of Cancer, J. Med. **14**:141-146, 1933. Rosenrauch, C.: A propos de l'érysipèle salutaire et de son action thérapeutique sur les tumeurs malignes, Clinique, Paris **28**:324-326, 1933. Fehleisen, F.: Die Aetiologie des Erysipels, Berlin, T. Fischer, 1883; cited by Coley. Coley, W. B.: The Treatment of Malignant Tumors by Repeated Inoculations of Erysipelas, with a Report of Ten Original Cases, Am. J. M. Sc. **105**:487-511, 1893. Lindenstein, L.: Bemerkungen zu der Arbeit von Prim. Dr. A. Mülleder: "Als Beitrag zum Kapitel Erysipel und Karzinom," Zentralbl. f. Chir. **59**:2531-2532, 1932. Mülleder, A.: Als Beitrag zum Kapitel "Erysipel und Karzinom," ibid. **59**:1684-1685, 1932. Lomer, R.: Zur Frage der Heilbarkeit des Carcinoms, Ztschr. f. Geburtsh. u. Gynäk. **50**:305-384, 1903. Mohr, H.: Ueber spontane Heilungsvorgänge beim Karzinom, Therap. Monatsh. **17**:553-560, 1903.

8. Theilhaber, A.: Zur Lehre von der Spontanheilung der Karzinome, Deutsche med. Wchnschr. **38**:1240-1241, 1912. Watson, J.: Butyric Acid in the Treatment of Cancer, Lancet **1**:746-748, 1933. Byrne, J.: A Digest of Twenty Years' Experience in the Treatment of Cancer of the Uterus by Galvano-Cautery, Am. J. Obst. **22**:1052-1053, 1889; Vaginal Hysterectomy and High Amputation, or Partial Extirpation by Galvanocautery in Cancer of Cervix Uteri: An Inquiry into Their Relative Merits, Brooklyn M. J. **6**:729-760, 1892; Tr. Am. Gynec. Soc. **17**:3-41, 1892.

been directly touched by the cautery or other agent. All these bizarre reports can be unified and utilized more intelligently with the understanding that the production of a certain kind and degree of inflammatory reaction is the essential basis of all effective treatment of this kind.

The principal new viewpoint to suggest, therefore, is that the examples of infectious cure of neoplasms have been in the main misinterpreted and that the curative agency which was sought in the form of a systemic intoxication is really to be found in the local inflammatory reaction. It is impossible to overlook the similarity of action of ligation, arsenic and streptococcus or other bacterial toxins in causing edema, inflammation, capillary permeability changes and sometimes hemorrhages. A severe local infection often creates tumefaction and induration, which is illustrated on a large scale in a carbuncle. The pressure and lack of circulation in the interior may reach the point of necrosis, but in the zones outside this there must also be an abnormal state of circulation and cell nutrition. This state of partial asphyxia seems to favor destruction of the tumor in somewhat the same way as does ligation. On the other hand, strong sodium chloride solutions and similar irritants produce an inflammatory area which is bright red throughout. This type of inflammation never destroys experimental tumors and may even hasten their growth, and the same may be true of some types of infection.

There appear to be at least five illustrations of efficient protection against tumors by local tissue reactions:

1. The local "immunity" conferred by light roentgen therapy against implantation of experimental cancer.[9]

2. The cure of certain cancers by local applications of arsenic and other chemicals. The mode of action of these substances is still uncertain. Granting, however, that there is a destruction of deep cells not in direct contact with the medicament, it seems scarcely probable that such a diverse group of substances should all be specifically toxic for tumor cells in distinction from normal cells; but all these substances share the common property of setting up inflammatory or tissue reactions, which may plausibly account for the selective tumor destruction.

9. Da Fano, C.: Zelluläre Analyse der Geschwulstimmunitätsreaktion, Ztschr. f. Immunitätsforsch. **5**:1-75, 1910. Murphy, J. B., and Sturm, E. J.: The Lymphocyte in Natural and Induced Resistance to Transplanted Cancer: Effect of Dry Heat on Resistance to Transplanted Cancer in Mice, J. Exper. Med. **29**:25-34, 1919. Murphy, J. B.: The Lymphocyte in Resistance to Tissue Grafting, Malignant Disease, and Tuberculous Infection, Monograph 21, Rockefeller Institute for Medical Research, 1926.

3. The cure of transplanted mouse tumors by injections of starch (Chambers and Grand [10]) through a lymphocytic reaction in line with earlier theories,[9] and the slightly different natural defensive reaction in resistant animals.[11]

4. The spontaneous recession or cure of malignant tumors in human patients,[12] sometimes under slight or unknown influences but mostly due directly to severe infection or inflammation.

5. The partial or complete breakdown of tumors following the asphyxia produced by ligation.

These reactions appear to differ in character and degree. Nos. 1 and 3 are mild in their effects and apparently feeble in potency; the tissue reaction to roentgen therapy [13] is not accepted by authorities as curative; the reaction to starch seems to cure only the highly sensitive mouse tumors, but some equally mild accidental reaction may have cured a few especially sensitive human tumors. The other curative reactions, to ligation, caustic applications and infections, are more violent and apparently more powerful. Arsenic may hold an intermediate place, since the ordinary arsenic pastes set up severe inflammation, but arsenic solutions cause minimal irritation, and in case 2 (this paper) it proved possible to cure a feeble tumor by arsenical infiltration together with partial anemia. It is only by rare accident or in the case of the feebler tumors that any of the aforementioned tissue reactions alone suffices to effect a cure. The best results seem to be promised by suitable combinations. To some extent every foreign or new growth seems susceptible to this form of attack. Thus, both tumor tissue and normal granulation tissue break down under ligation, and when a tumor is converted into an inflamed mass by repeated injections of toxin a roentgen treatment liquefies the tumor and the inflammatory exudate but not the normal tissues.

Obviously, this entire work is strictly in an experimental stage. Extensive research is necessary to discover the nature and the most favorable forms and combinations of the agents for provoking tissue reaction. Actual ligation is seldom applicable, and, though the possibility has been suggested for certain bone sarcomas, many contingencies

10. Chambers, R., and Grand, C. G.: The Effect of Injecting Starch Grains into Transplanted Tumors, Am. J. Cancer **29**:111-115, 1937.

11. Roussy, G.; Leroux, R., and Peyre, E.: Le cancer de goudron chez la souris, Presse méd. **30**:1061-1065, 1922.

12. Footnotes 6 and 7.

13. (*a*) Sittenfield, M. J.: A Method to Render Radioresistant Tumors Radiosensitive, Radiology **22**:490-492, 1934. (*b*) Allen, F. M.: Local Asphyxia and Roentgen Irradiation of Transplantable Rat Tumors, Am. J. Roentgenol. **42**:745-755, 1939.

of failure or danger must be gravely considered. It seems justifiable to make tests of isolated superficial nodules in cases of inoperable tumor in order to learn the response of different tumor types, with the foreknowledge that problems of technic remain to be solved and that some tumors may prove entirely resistant. The combination of toxic inflammation and roentgen therapy [13b] may approach closer to practical application, for example, in breaking down gross masses, as has been suggested. Furthermore, when a surgeon removes a radioresistant tumor and suspects metastases in a definite area, he commonly goes through the ceremony of ordering roentgen treatment, hoping that it will help while knowing that it will not. It is theoretically possible that the production of a suitable kind and degree of inflammation may sensitize the subject in such a manner that the roentgen rays can actually kill metastases in certain regions, for example, the chest wall, the neck or the pelvis.

SUMMARY AND CONCLUSIONS

Resistance to asphyxia varies with the type of tumor and perhaps with the animal species but not in any uniform way with the foreign or native origin of the tumor. Some spontaneous tumors are far more easily cured by asphyxia than are some transplanted tumors.

An account is given of 2 patients in whom tumors were treated by asphyxia or by chemical methods aimed to produce similar local reactions. The tumor in 1 of the cases was highly resistant. In the other case, the main mass of a squamous cell carcinoma of the skin was made to disappear by temporary asphyxia, and a similar result occurred in the remaining portion after infiltration of a nonirritant arsenic solution under such pressure as to maintain relative anemia for a period.

The principal general deductions are (*a*) that the great mass of nonoperative cures or recessions of malignant tumors reported in the literature can be brought into unified comprehension on the basis of a reaction in the normal tissues, usually associated with inflammation, and (*b*) that the cure of properly selected tumors may sometimes be favored by the adjuvant action of two or more agents tending to set up this reaction. Further investigation along this line is believed to be warranted not only by the present results but by this interpretation of the literature.

SPLENECTOMY IN THE TREATMENT OF BANTI'S SYNDROME

E. H. BARG, M.D.
AND
J. W. DULIN, M.D
IOWA CITY

Since 1922, 43 patients have fulfilled the requirements for a diagnosis of Banti's syndrome at the State University Hospitals. Half of these patients were treated by splenectomy, and the remainder were treated conservatively. A comparison of the two groups was made in an effort to determine the effects of splenectomy.

This syndrome was separated from other splenic enlargements by Banti [1] in 1883, 1894 and 1910 and is frequently spoken of as Banti's disease. In 1900, Osler [2] reported a series of cases of a similar condition, which he called splenic anemia. The two terms are used interchangeably both in the United States and on the Continent. The English and German authors reserve the term Banti's disease for the advanced condition, with marked cirrhosis of the liver. American writers also include under the terms splenic anemia and Banti's disease splenomegaly with anemia caused by syphilis, tuberculosis and malaria.

The cause of Banti's disease is unknown. Banti and many workers (Yates, Bunting and Kristjanson,[3] Gibson [4] and Peel [5]) have attempted the isolation of causative micro-organisms. Recent etiologic theories include circulatory obstruction, such as direct or indirect stasis of the splenic vein as described by Rousselot [6] in 1936.

In this series there were no specific pathognomonic changes in the spleen. The spleen retained its normal gross contour. In the cases in which we operated the average weight of the organ was 800 Gm. The

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From the Department of General Surgery, State University Hospitals.

1. Farley, D. L.: Banti's Disease, in Piersol, G. M.; Bartz, E L., and others: Cyclopedia of Medicine, Philadelphia, F. A. Davis Company, 1932, vol. 6, p. 680.

2. Osler, W.: Am. J. M. Sc. **119**:54, 1900.

3. Yates, J. L.; Bunting, C. H., and Kristjanson, H. T.: The Etiology of Splenic Anemia or Banti's Disease, J. A. M. A. **63**:2225 (Dec. 19) 1914.

4. Gibson, A. G.: Quart. J. Med. **7**:153, 1914.

5. Peel, A. A. F.: J. Path. & Bact. **31**:591, 1928.

6. Rousselot, L. M.: Rôle of Congestion (Portal Hypertension) in So-Called Banti's Syndrome: Clinical and Pathologic Study of Thirty-One Cases with Late Results Following Splenectomy, J. A. M. A. **107**:1788 (Nov. 28) 1936.

surface was usually covered with vascular adhesions, and the capsule was markedly thickened. There was an increased amount of fibrous tissue in the splenic framework and pulp. Frequently the splenic vein showed evidences of phlebitis, thrombosis or phlebosclerosis. We have observed at the time of operation several instances in which the splenic vein was greatly enlarged. On microscopic examination of the spleen there was marked fibrosis; the malpighian bodies were small and widely separated, and siderotic nodules were frequent. In the liver varying degrees of lobular cirrhosis were observed.

Since Banti's original description the disease has been divided into three stages. In the first stage the patient has splenic enlargement with or without mild secondary anemia. It has been thought that this stage lasts from three to five years. The second stage follows, is transitory and consists of increase of the symptoms and signs observed in the first stage plus hepatic enlargement, occasional attacks of icterus and pain in the upper part of the abdomen. In the third, or terminal, stage the hepatic symptoms predominate, with the appearance of ascites and esophageal or gastric hemorrhages. Because of the difficulty in the division of these stages, a more satisfactory classification divides the disease into a nonascitic and an ascitic stage.

Although in this series the syndrome usually appeared in the third decade of life, the patients varied from 5 to 75 years of age, 6 being children under 16 years of age. The average age of the surgically treated group was 35 years, and that of the group on whom no operation was performed was 43 years. The two sexes were about equally affected. The duration of symptoms averaged five years in the group on whom splenectomy was performed and four years in the group that did not undergo splenectomy.

The onset of the symptoms was often insidious. Gastroesophageal hemorrhages were often the first manifestation of the disease. Such hemorrhages are due to a rupture of gastroesophageal varices and may be small and repeated or massive with occasional exsanguination. The diagnosis of hemorrhage may be based on hematemesis or on the finding of blood in the stools. In our series 39 per cent of the patients had hematemesis. This represents a smaller per cent of cases of bleeding from varices than was reported in Chaney's [7] or Pemberton's [8] series. Epistaxis occurred in 25 per cent of the cases. Owing to the perisplenitis, recurring attacks of pain in the left upper abdominal quadrant were frequent. Occasionally the patient complained of gradually increasing size of the abdomen, due to the enlarged spleen, to the enlarging liver,

7. Chaney, W. C.: Am. J. M. Sc. **165**:856, 1923.

8. Pemberton, J. de J.: Ann. Surg. **94**:755, 1931.

to ascites or to a combination of the three. Edema of the lower extremities occurred late in the course of the disease. Icterus rarely appeared. Low grade fever, with temperatures varying from 100 to 102 F., was present in 32 of the cases.

The degree of anemia increased with the duration of the disease and the frequency of hemorrhages. The average red blood corpuscle count was 2,930,000 per cubic millimeter, and the hemoglobin content of the blood was 50 per cent of the normal. In addition to the anemia there were associated leukopenia and relative lymphocytosis. The average leukocyte count was 3,700 per cubic millimeter, with relative lymphocytosis in 15 instances. Lymphocytosis (50 to 60 per cent lymphocytes) was common. In 47 per cent of cases the blood platelet count was below normal. The coagulation time, bleeding time, clot retractility and fragility of the red blood corpuscles were within normal limits. In 3 instances the Wassermann reaction of the blood was positive for syphilis. The condition in these cases was classified as syphilitic Banti's disease, and the patients received treatment for syphilis in addition to splenectomy.

The diagnosis is usually made by exclusion. Among the more common entities which may simulate the condition are the leukemias, Hodgkin's disease, familial and acquired hemolytic icterus, pernicious anemia, thrombopenic purpura, Gaucher's disease and Niemann-Pick disease. In cases of cirrhosis of the liver with secondary splenomegaly it may be impossible to differentiate the two conditions. It is thought that in the last-mentioned condition the cirrhosis is primary and the splenic enlargement is secondary. Occasionally, differentiation between early Banti's disease and unusual types of tumor masses in the left upper abdominal quadrant is difficult. Retroperitoneal sarcoma, hypernephroma, pancreatic tumor and enlargement of the left lobe of the liver have been confused preoperatively with splenomegaly. Our demonstration of the splenic notch by physical examination was inaccurate in many of these cases.

Splenecetomy was performed on 22 patients, with 6 operative deaths. Postmortem examinations were performed on all 6. Three of the deaths occurred in patients over 60 years of age. In 3 of the 6 the disease was in the nonascitic stage. Three of the deaths were a result of hemorrhage occurring from the operative site. One patient, who died on the eighth postoperative day, was found to have massive thrombosis of the superior and inferior mesenteric veins. In 1 instance death occurred on the tenth postoperative day as a result of multiple pulmonary infarcts. In the sixth instance, death (of a patient 66 years of age) was due to cardiac failure. Two additional patients died in the hospital.

In 1 instance death was due to hemorrhage from the deep epigastric vessels following a paracentesis. In the other the patient died two months postoperatively of a massive hemorrhage from a ruptured esophageal varix.

Of the 14 patients who left the hospital, 12 have been followed. At the time of writing, 3 have died from gastroesophageal hemorrhage and 1 from an unknown cause. Four are alive and have been free of all symptoms for nine years, seven years, five years and two years since splenectomy. Two are much improved after three years and one year respectively, their only complaints being weakness and malaise. One of the remaining 2 patients states that she is symptomatically well; however, she has had occasional esophageal hemorrhages during the ten years following splenectomy. The remaining patient has lived five years and in this interval has had several minor esophageal hemorrhages and requires frequent paracentesis. Two of the 5 patients who preoperatively had gastroesophageal hemorrhages have continued to have such hemorrhages. In 4 patients this symptom developed for the first time after splenectomy, resulting in death in 3 instances. One of these is of interest because the hemorrhage first appeared eight years after operation.

Splenectomy had a favorable influence on ascites. Of 6 patients who preoperatively had required repeated paracentesis, only 1 has continued to have reaccumulations of abdominal fluid. The others have had no recurrence for seven years, five years, three years, two years and one year respectively. In the nonascitic group no instance of ascites occurred postoperatively.

There were no permanent ill effects attributable to removal of the spleen. The blood platelets rapidly rose, occasionally to 2.5 per cent volumetrically, and gradually returned to a relatively normal level over a period of weeks. The red blood corpuscles were temporarily increased. The early leukocytic response varied, the counts ranging from 15,000 to 40,000 white blood cells per cubic millimeter, with a decline to normal within four weeks. In a few instances there was a slight increase in the fragility of the red blood corpuscles.

Of the 21 patients on whom splenectomy was not performed, 6 are known to be living. Two have had fair general health for nine years and four years respectively. The latter has an occasional small gastroesophageal hemorrhage. In the remaining 4 cases the condition was diagnosed within the last two and one-half years. Two of the patients have had a progressive increase in their symptoms. Eleven of this group are known to be dead. One lived for three years, and all the others died within one year after discharge from the hospital.

COMMENT

From our review of these cases of Banti's disease, we believe that splenectomy is the treatment of choice and should be performed in the early stages. The procedure may be contraindicated for elderly patients because of the high operative mortality. However, 3 of our patients who were over 60 years of age have been greatly improved after operation. In our experience splenectomy, for some unexplainable reason, has relieved the patients of their ascites. Whether this is due to a lessening of the circulatory load through the liver has not been proved. Undoubtedly, an extensive collateral circulation is developed between the region of the splenic bed and the abdominal parietes. We do not perform an omentopexy, although in some of our recent cases the greater omentum has been rotated into the splenic bed, as it is felt that this increases the collateral circulation. Splenectomy has not assured relief of gastroesophageal hemorrhages. In general, patients with rapidly developing symptoms before operation respond poorly to splenectomy.

SUMMARY

Forty-three cases of Banti's syndrome were reviewed.

Splenectomy was performed on 22 patients.

There was an operative mortality of 27 per cent.

Hemorrhage from the operative site accounted for 50 per cent of the mortalities.

Duration of life was prolonged after splenectomy.

Ascites was relieved after splenectomy.

Gastroesophageal hemorrhages frequently continued or appeared for the first time after splenectomy.

DEMONSTRATION OF A CAPILLARY PERMEABILITY FACTOR IN TISSUE EXTRACTS FROM NORMAL RABBITS

R. H. RIGDON, M.D.
NASHVILLE, TENN.

Recently it has been shown that trypan blue after intravenous injection localizes and concentrates in areas of inflammation produced by the local application of xylene in the rabbit's skin only when the dye is given immediately or within approximately three hours after application of the irritant. Three hours after application of the xylene the skin shows all the cardinal features of inflammation. A second application of xylene to this area of inflammation immediately before the intravenous injection of trypan blue apparently produces some change in the tissues and capillaries that permits the localization and concentration of the dye in the area.[1]

The studies of Rous and Smith[2] have shown that colloidal dyes escape from the capillaries in the skin and the adjacent part of the venules. A definite gradient of permeability occurs in the small blood vessels. After local application of an irritant the dye escapes from a larger portion of these same vessels than occurs under normal conditions. The rapid accumulation of trypan blue in areas of skin recently treated with xylene suggests either that xylene acts directly on these capillaries and venules or that an intermediate substance is liberated by the tissue which acts on the endothelium of the capillaries to make them more permeable to this colloidal dye.

The failure of trypan blue to localize and concentrate in the skin after an intradermal injection of xylene may indicate that the substance responsible for the increase in capillary permeability is present only in the squamous epithelium. At least, it appears that it is present in a greater quantity in the epithelium than in the dermis.

From the Department of Pathology, Vanderbilt University Medical School.

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1. Rigdon, R. H.: Capillary Permeability in the Skin of the Rabbit, Proc. Soc. Exper. Biol. & Med. **42**:43-45, 1939.

2. Rous, P., and Smith, F.: The Gradient of Vascular Permeability: Gradient Along Capillaries and Venules of Frog Skin, J. Exper. Med. **53**:219-242, 1931.

This theoretic substance differs from leukotaxine in that it is present in saline extracts from normal tissue, while leukotaxine occurs only in areas of inflammation, according to Menkin.[3]

The present study is a report of the demonstration of a substance obtained from a saline extract of normal rabbit tissues which will produce an increase in capillary permeability after intradermal injection in the rabbit, as shown by the localization and concentration of trypan blue.

MATERIAL AND METHODS

The tissues which have been most frequently studied are skin, muscle and testicle. These are cut into small pieces and then pounded in a mortar with a pestle. Saline solution is added during this process of maceration. The extracts are then centrifuged, and the supernatant fluid is used for intradermal injection into the skin of normal rabbits.

In the earlier preparation of the extract no definite quantity of either tissue or saline solution was used; however, in the later experiments the following arbitrary amounts were employed:

	Group A		Group B	
Tissues	Weight, Gm.	Saline Solution, Cc.	Weight, Gm.	Saline Solution, Cc.
Testicle...	1.0	15	2.3	15
Skin.....	12.6	20	19.0	20
Muscle....	12.6	25	10.0	20

To compare the crude leukotaxine which Menkin [3] obtained from inflammatory exudates with the extracts of normal tissue, 0.7 cc. of a 10 per cent concentration of croton oil in olive oil was injected into the left pleural cavity of the same rabbit from which the tissues were removed from group B. The oil was injected forty-three hours before the animal was killed. Approximately 45 cc. of cloudy straw-colored fluid was aspirated from the pleural cavity. This fluid was centrifuged, and the supernatant liquid was tested for the permeability factor. The control preparation for the pleural exudate was made by thoroughly mixing 0.7 cc. of the same croton oil–olive oil mixture with 45 cc. of saline solution.

The rabbits were carefully shaved twenty-four hours before the "difference preparations" were injected intradermally. Two-tenths cubic centimeter of the extract liquid was injected at different intervals before 10 to 15 cc. of either a 0.2 per cent or a 0.4 per cent solution of trypan blue was injected into the veins of the ear. The skin was carefully observed before and after injection of the dye. Some of the animals were killed, and histologic sections were made from the skin to study the relation of the local accumulation of leukocytes to the localization and concentration of trypan blue.

EXPERIMENTS

Two rabbits were given injections of 0.2 cc. of the three tissue extracts in group A at the following intervals before 10 cc. of a 0.2 per cent suspension of trypan blue was given intravenously: area 1, three hours; area 2, two hours, and area 3, one hour. In area 4 the injection was given immediately before injection of the dye. Twenty-five minutes later trypan blue was present in areas 2, 3 and 4

3. Menkin, V.: Studies on Inflammation, J. Exper. Med. **64**:485-502, 1936.

where the skin extract had been injected and only in areas 3 and 4 where the testicle extract had been given. No dye was present in any of the four areas where the muscle extract had been injected.

The three tissue extracts in group A were diluted in saline solution as follows: 1:10, 1:100 and 1:1,000. Two-tenths cubic centimeter of each was then injected into the skin of the same 2 rabbits approximately thirty minutes before the dye was given. Twenty-five minutes later a small amount of trypan blue was present in the areas where the 1:10 dilution of both the cutaneous and the testicular extracts had been injected in 1 of the 2 rabbits. No dye was present in either of these areas in the second rabbit. No dye was present in any of the areas where the muscle extract had been injected in either of the 2 animals.

One cubic centimeter of each of the three extracts in group A was placed in each of four test tubes (1 by 10 cm.). These were then placed in a large boiler of water, and the temperature was gradually brought to 60 C. Ten minutes later one tube of each series was removed; after thirty minutes a second was removed, after forty minutes a third was removed and after sixty minutes the fourth was removed. The extract of muscle was coagulated when the first tube was removed from the water bath. The extracts of skin and of testicle became cloudy at this time, but they never coagulated. Two-tenths cubic centimeter of these heated tissue extracts was then injected intradermally into the same 2 rabbits approximately thirty minutes before the trypan blue was injected. Twenty-five minutes later the dye was present in all of the areas into which the heated cutaneous and testicular extracts had been injected in rabbit 1, while no dye was present in either of the areas in the second rabbit. It is obvious from these experiments that rabbits vary in their susceptibility to the substance responsible for the increase in capillary permeability.

The tissue extracts in group A were injected intravenously into 2 rabbits to study their effect on the blood pressure. The rabbits were anesthetized with pentobarbital sodium, and a cannula was put into the carotid artery. One and five-tenths to 4 cc. of the different extracts was injected into the marginal veins of the ear. The blood pressure was not affected by any of the extracts.

There was a variation in the rate of diffusion in the tissues of the different extracts. When testicular extract was injected intradermally the bleb rapidly disappeared. The area of blue which developed after injection of trypan blue progressively increased in size in the areas where testicular extract was injected. Trypan blue localized first and the greatest quantity in the areas of skin treated with the skin extract; however, the dye did not spread as it did in the area treated with testicle. This variation in the localization of trypan blue in areas of skin treated with injected testicle extract as compared with skin extract is interesting in view of the characteristics attributed to testicular extracts by Hoffman and Duran-Reynals.[4]

The results obtained from the injection of the extracts in group B into 2 rabbits were the same as those observed with the extracts in group A. Trypan blue localized in the areas of skin treated with the skin and testicle extracts but did not localize where either the muscle extract or the pleural exudate had been injected. The dye did localize, however, in the areas where the saline suspension of croton oil and olive oil had been injected. These 2 rabbits were killed sixty minutes after injection of the trypan blue, and sections of skin were removed

4. Hoffman, D. C., and Duran-Reynals, F.: The Influence of Testicular Extract on the Intradermal Spread of Injected Fluids and Particles, J. Exper. Med. **53**:387-398, 1931.

from the four areas treated with the extract of skin and from the four areas treated with the extract of muscle. There was a greater number of leukocytes in the tissue where the skin extract had been injected than there was in the areas of tissue treated with the muscle extract even in the same rabbit. There were essentially no leukocytes in the tissue where the extract of skin had been injected immediately before the dye was given. A tremendous number of polymorphonuclear leukocytes were present, however, in the area where the skin extract had been injected two and a half hours before the dye was given. As has been stated, trypan blue did not concentrate in the areas treated with the cutaneous extract two and a half hours prior to injection of the dye.

Skin from a normal rabbit was macerated in saline solution and centrifuged, and the supernatant fluid was filtered through a Berkefeld V candle. This sterile filtrate contained a substance that produced an increase in capillary permeability. Saline extracts of the liver and kidney also showed in the supernatant fluid a little of the substance which produces an increase in capillary permeability. The quantity, however, was much less than that present in extracts of the skin and testicle.

COMMENT

The demonstration of a substance in the saline extract of normal rabbit tissue that produces an increase in the permeability of the capillaries in the skin of the rabbit is interesting in view of Menkin's work on leukotaxine. My results confirm those of Bier and Planet.[5]

Leukotaxine, according to Menkin,[3] is obtained from tissue that is the site of an inflammatory reaction. When injected intradermally it causes an increase in permeability as shown by the localization and concentration of trypan blue, and also it produces a rapid emigration of leukocytes into the part. Leukocytes also appear in the tissue where the extract of normal skin is injected; however, when the greater number of leukocytes are present trypan blue fails to concentrate in the area. The fact that trypan blue fails to localize and concentrate in all areas of inflammation produced by xylene suggest that the mechanism by which the capillaries become more permeable may not be the same as that responsible for the localization of leukocytes in areas of inflammation. The two processes may, however, occur together.

The failure of trypan blue to concentrate in areas of skin treated with injected extracts of skin and muscle when the dye is injected three hours after intradermal injection of the extracts is interesting in view of previous experiments, in which xylene was applied to the skin.[6] These have shown that trypan blue does not concentrate in xylene-treated areas of skin when it is given intravenously approximately three hours after application of the irritant.

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5. Bier, O., and Planet, N.: Sur la présence d'un facteur qui augmente la permeabilité capillaire dans les extraits de peau normale, Compt. rend. Soc. de biol. **129**:65-67, 1938.

6. Rigdon, R. H.: Capillary Permeability in Areas of Inflammation Produced by Xylene, Arch. Surg., this issue, p. 101.

The wide variation in amount of the permeability factor in the different tissues suggests that the failure of trypan blue to localize in an area where xylene is injected intradermally may be due either to the small quantity of this substance liberated from the tissue in the subdermis or that the capilaries are too few in this area to permit escape of a sufficient quantity of the dye to color the tissue.

It is possible that the same permeability factor may be present in both the cutaneous and the testicular extract. The variation in staining of the area with trypan blue may result from a difference in diffusion of the two extracts. The testicular extract may contain one or more substances that influence the rate of diffusion and only one that produces an increase in permeability of the capillaries.

The capillary permeability factor present in the extracts of skin and testicle resembles the spreading factor of Duran-Reynal in that both are thermostable and filtrable. These tissue extracts when injected intravenously in normal rabbits have no effect on the blood pressure. Leukotaxine, according to Menkin, may produce either no change or only a transient and practically negligible fall in the cat's blood pressure.[7]

Trypan blue, when given intravenously after the intradermal injection of 2 mg. of histamine diluted with distilled water, localizes about the margin of the bleb. The same dye localizes in the center of the areas treated with the injected extracts of skin and testicle. Subsequent studies will be necessary before any comparison of the substance obtained from saline extracts of normal skin and normal testicle can be made with histamine and leukotaxine. These crude extracts of normal rabbit tissue will be purified according to the method used by Menkin [8] to obtain crystalline leukotaxine.

SUMMARY

A substance has been obtained from the skin, muscle and testicle of normal rabbits which produces a local increase in capillary permeability, as manifested by the localization and concentration of trypan blue. This substance is obtained by macerating normal tissue in saline solution.

7. Menkin, V., and Kadish, M. A.: Studies on the Physiological Effects of Leukotaxine, Am. J. Physiol. **124**:524-529, 1939.

8. Menkin, V.: Studies on Inflammation, J. Exper. Med. **67**:129-144, 1938.

CAPILLARY PERMEABILITY IN AREAS OF INFLAMMATION PRODUCED BY XYLENE

R. H. RIGDON, M.D.
NASHVILLE, TENN.

The smaller blood vessels in areas of inflammation show an increase in permeability as manifested by an increase in the flow of fluid from the capillaries into the tissue spaces. This increase in permeability may also be shown by the localization and concentration of colloidal dyes. Many investigators [1] have observed the localization and concentration of blood-borne material in areas of inflammation. Burrows [2] has recently stated that "whenever inflammation occurs and from whatever cause, an increased permeability of the capillaries may be expected." Menkin [3] has also frequently emphasized the fact that trypan blue and other dyes after intravenous injection promptly accumulate in areas of inflammation.

Recently I reported that trypan blue and india ink do not always concentrate in areas of inflammation produced by local application of xylene to the skin of rabbits.[4] These substances concentrate in such areas only when they are injected into the circulation immediately or within less than five hours after application of the xylene. The skin treated with this irritant after five hours shows all the macroscopic and microscopic changes associated with inflammation.

In the present study observations have been made on the localization (after intravascular injection) of trypan blue, india ink, antitoxin and vaccine virus in the areas of inflammation produced by local application of xylene to the skin of the rabbit.

From the Department of Pathology, Vanderbilt University Medical School.

Aided by a grant from the Division of Medical Sciences, Rockefeller Foundation.

1. (*a*) Kettle, E. H.: The Demonstration by the Fixation Abscess of the Influence of Silica in Determining B. Tuberculosis Infections, Brit. J. Exper. Path. **5**:158-164, 1924. (*b*) Hanger, F. M., Jr.: Effect of Intravenous Bacterial Filtrates on Skin Tests and Local Infections, Proc. Soc. Exper. Biol. & Med. **25**:775-777, 1928. (*c*) Menkin, V.: The Accumulation of Iron in Tuberculous Areas, ibid. **27**:1020-1022, 1930; Studies on Inflammation, J. Exper. Med. **50**: 171-180, 1929.

2. Burrows, H.: Some Factors in the Localisation of Disease in the Body, Baltimore, William Wood & Company, 1932.

3. Menkin, V.: Role of Inflammation in Immunity, Physiol. Rev. **18**:366-418, 1938.

4. Rigdon, R. H.: Capillary Permeability in the Skin of the Rabbit, Proc. Soc. Exper. Biol. & Med. **42**:43-45, 1939.

LOCALIZATION AND CONCENTRATION OF TRYPAN BLUE IN XYLENE-TREATED AREAS OF SKIN

Xylene was applied on a cotton swab to areas of normal skin. The degree of injury produced by this irritant is relatively uniform in the different areas of the same rabbit and also in different rabbits. Xylene was applied to the skin of a single rabbit at intervals varying from immediately to forty-eight hours before the dye was injected. The skin usually became hyperemic within two or three minutes after application of this irritant, and frequently it was edematous within ten minutes. The edema and hyperemia remained for several days, after which time the epithelium desquamated. Polymorphonuclear leukocytes apparently began to infiltrate the dermis within ten to fifteen minutes after the xylene was applied. Usually one and a half or two hours elapsed, however, before any significant number of leukocytes reached this tissue. Polymorphonuclear leukocytes and mononuclear cells continued to infiltrate the xylene-treated areas for ten to twelve hours. At this time many of the superficial epithelial cells were pyknotic and necrotic. Small groups of these epithelial cells separated from the basement membrane, and the spaces were filled with fluid and leukocytes. After thirty hours many of the epithelial cells were necrotic. The leukocytic exudate apparently did not increase after this time.

The trypan blue was suspended in saline solution. Usually 10 cc. of a 0.2 per cent solution was given intravenously. The marginal veins of the ears were used for these injections. Only macroscopic observations were made in determining the presence of trypan blue in the xylene-treated and in the untreated areas of skin. The xylene-treated skin became dark blue within five minutes when the dye was injected immediately after application of the xylene. When the irritant was applied twenty-four hours before the dye was injected the xylene-treated areas of skin stained the same color as the untreated skin. When xylene was applied to different areas of the skin of a single rabbit at ten minute intervals, trypan blue localized first and in greatest quantity in the area where the irritant was last applied before the dye was given intravenously. The relation of the time of localization of trypan blue after an intravenous injection to the application of xylene is shown in figure 1. Xylene was applied to the skin in area 1 ninety minutes before the dye was injected intravenously; in area 2, sixty minutes; in area 3, thirty minutes; in area 4, fifteen minutes; in area 5, five minutes, and in area 6, immediately before the dye was given. This photograph was made eight minutes after injection of the dye. At this time the greatest amount of trypan blue was present in area 6. There was a progressive diminution in the amount of dyes in areas 5, 4, 3 and 2. No dye was present at this time in area 1.

In this experiment the interval between the first application of xylene and the injection of trypan blue was too short to provide any accurate information with regard to the relation between edema and hyperemia and the localization of trypan blue. Xylene was similarly applied to the skin of another group of rabbits at intervals longer than those in the preceding experiment. The irritant was applied to the skin of 1 of these animals at the following time before the dye was injected intravenously: area 1, twenty hours; area 2, two and one-quarter hours; area 3, forty-six minutes, and area 4, four minutes. Edema and hyperemia were present in areas 1, 2 and 3 when the trypan blue was injected. One hour after the dye was given there appeared to be the same amount of dye in areas 1 and 2 as there was in the untreated skin. Areas 3 and 4 were dark blue at this time.

Xylene was injected intradermally in a group of rabbits. Edema and hyperemia were present twenty-four hours after an intradermal injection of 0.2 cc. of this irritant. These areas after twenty-four to forty-eight hours showed necrosis of the subdermal tissue. Trypan blue when injected intravenously failed to localize in the areas where xylene was injected intradermally, although the dye was given immediately after injection of the xylene. This dye also failed to localize and concentrate in the areas of inflammation when the xylene was injected twenty-four hours previously.

Trypan blue will localize in areas of skin where xylene is applied twenty-four hours previously provided a second application of the irritant is made immediately before the dye is given. This dye also localizes and concentrates in the skin in areas where xylene is injected intradermally twenty-four hours previously if the irritant is also applied to the skin over the edematous and hyperemic areas immediately before the dye is given intravenously.

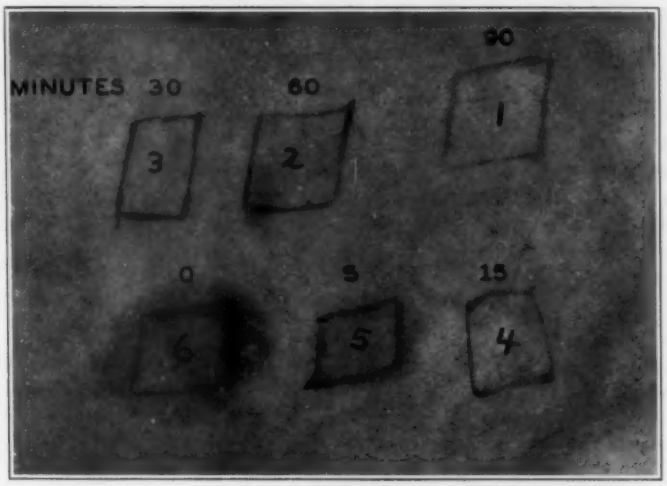

Fig. 1.—The number above each square gives the time in minutes that xylene was applied before 10 cc. of 0.2 per cent trypan blue suspended in saline solution was injected intravenously. The number of the square is shown in the center of each. This photograph was made eight minutes after the dye was injected. The largest amount of trypan blue localizes in the area where xylene was last applied.

LOCALIZATION AND CONCENTRATION OF INDIA INK IN XYLENE-TREATED AREAS OF SKIN

India ink was used in this part of the experiment to determine whether it will localize and concentrate in areas of inflammation produced with xylene in a manner similar to that previously observed with trypan blue. Higgin's india ink was diluted in saline solution, and the carbon suspension was injected into the left ventricle of the rabbit's heart. The quantity and concentration of the carbon suspension varied with the different animals. Some of the rabbits died immediately after injection of the ink, while others survived from five to sixty minutes. Some of the rabbits were observed for five days, after which time they were discarded.

Sections of the xylene-treated and of the untreated skin were removed and fixed in solution of formaldehyde. Paraffin sections were prepared and stained both with hematoxylin and eosin and with trinitrophenol. Portions of the different sections of skin were cleared in benzene and methyl salicylate to demonstrate the carbon particles in the capillaries.

Carbon particles suspended in saline solution localize and concentrate in areas of inflammation produced with xylene only when the suspension is given immediately or only a short time after application of the irritant. Macroscopic and microscopic studies show that the carbon particles circulate through the blood vessels in the normal skin and in all the areas of inflammation produced by xylene. The carbon concentrates only in areas where the irritant is applied a short time before the ink is injected. The carbon particles appear either to stick or to be phagocytosed by the endothelial cells in the small blood vessels. Only a few of the minute carbon particles ever reach the extravascular spaces. Polymorphonuclear leukocytes phagocytose some of the small carbon particles and apparently carry them into the extravascular tissues.

LOCALIZATION AND CONCENTRATION OF ANTITOXIN IN XYLENE-TREATED AREAS OF SKIN

Staphylococcus and diphtheria antitoxins were injected intravenously in different groups of rabbits in which the skin had been previously treated with xylene. The presence of antitoxin in the skin is determined by either absence of necrosis or a diminution in the size of the necrotic area at the point of injection of the toxin. The toxin was injected into both xylene-treated and the untreated areas of skin of the same rabbit. One-tenth cubic centimeter of four different dilutions of the diphtheria toxin was injected intradermally. The degree of necrosis was compared in the treated with that in the untreated area of skin.

Five cubic centimeters (approximately 1,750 units) of staphylococcus antitoxin was given intravenously, and xylene was immediately applied to an area of skin approximately 4 by 6 cm. One-tenth cubic centimeter of staphylococcus toxin was then injected intradermally into the xylene-treated and the untreated skin at intervals up to nine days. The same degree of necrosis occurred in the xylene-treated and in the untreated areas of skin when the toxin was injected intradermally, immediately after intravenous injection of antitoxin. When the toxin was injected intradermally from three and one-quarter to forty-four hours after intravenous injection of antitoxin there was a marked diminution and sometimes complete inhibition of the necrosis in the xylene-treated areas of skin as compared with the necrosis in the untreated skin of the same rabbit. Control experiments have shown that this inhibition of necrosis does not occur in rabbits with a similar inflammatory process and no antitoxin. When the staphylococcus toxin is injected into the xylene-treated area eight days after intravenous injection of the antitoxin, a similar degree of necrosis occurs in both the xylene-treated and the untreated areas of skin (fig. 2).

In this experiment with staphylococcus antitoxin no attempt was made to determine the length of time that could elapse between application of the xylene and intravenous injection of the antitoxin before the latter would cease to localize and concentrate in the areas of inflammation. This observation was made, however, with diphtheria antitoxin by the injection of 0.4 to 0.6 cc., approximately 1,000 units, at different intervals after application of xylene to the skin.

A group of 3 rabbits was given diphtheria antitoxin intravenously, and xylene was applied immediately thereafter to the skin. These animals showed a marked

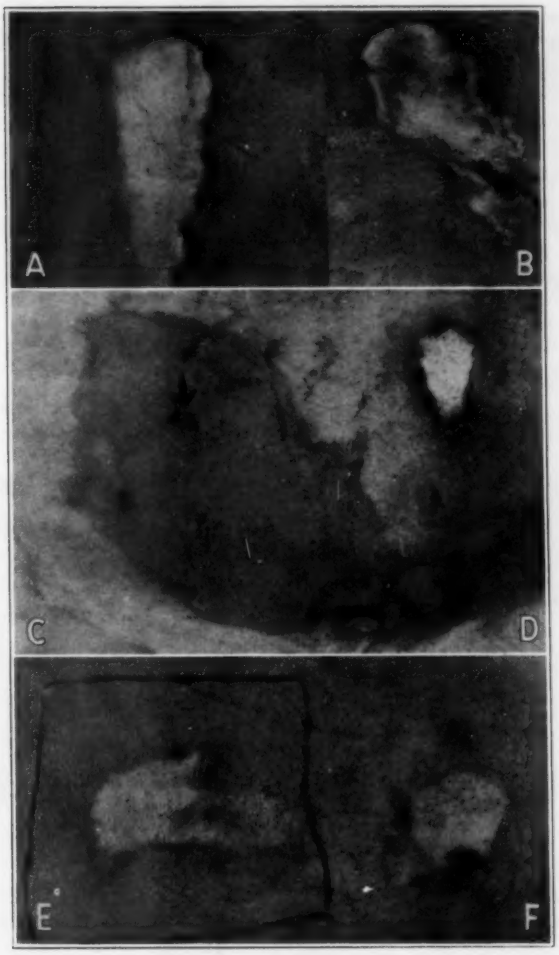

Fig. 2.—*A*, xylene was applied in the area outlined with india ink. Five hours later 0.1 cc. of staphylococcus toxin was injected intradermally. Extensive necrosis was present after twenty-four hours. *B*, an equal amount of toxin was injected intradermally in an area of the skin of the rabbit shown in *A*. Approximately the same degree of necrosis occurred in the untreated as in the treated skin. *C*, xylene was applied to the area of skin that is demarcated from the normal by the zone of hyperemia forty-four hours before 0.1 cc. of staphylococcus toxin was injected intradermally at the point indicated by the arrow. Essentially no necrosis occurred where the toxin was injected. *D*, a similar amount of toxin was injected into an area of untreated skin of rabbit shown in *C*. A large area of necrosis was present after twenty-four hours. *E*, xylene was applied in the area outlined with india ink nine days before 0.1 cc. of staphylococcus toxin was injected intradermally. There was no edema or hyperemia present when the toxin was injected. Extensive necrosis occurred within twenty-four hours. *F*, a similar quantity of toxin was injected into an area of untreated skin of rabbit shown in *E*. An area of necrosis approximately the same size as that in the skin treated with xylene is present after twenty-four hours.

decrease in the size of the areas of necrosis produced by diphtheria toxin in the xylene-treated skin as compared with the necrosis in the untreated skin. The diphtheria toxin was given intradermally immediately after injection of the antitoxin. A second group, of 4 rabbits, was given the same quantity of diphtheria antitoxin, and immediately thereafter xylene was applied to the skin. Different dilutions of diphtheria toxin were injected intradermally four to six hours later. The necrosis in these animals was much less in the xylene-treated areas than in the normal skin. A third group of rabbits was given diphtheria antitoxin eighteen to twenty-four hours after application of xylene. Diphtheria toxin was injected intradermally four to six hours later. The areas of necrosis in these rabbits were approximately the same in the xylene-treated as in the untreated skin.

LOCALIZATION OF VACCINE VIRUS IN XYLENE-TREATED AREAS OF SKIN

A suspension of virus was prepared by macerating in saline solution the growth obtained from the membrane of a chick embryo. The larger particles were

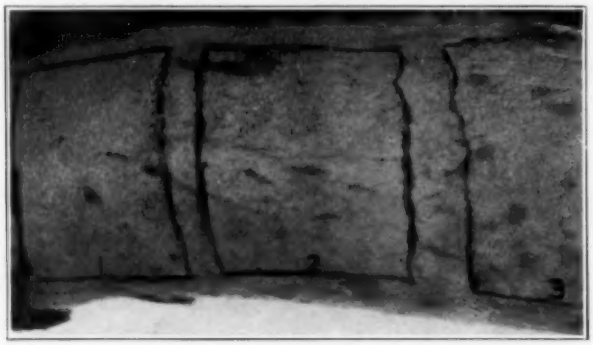

Fig. 3.—Xylene was applied in area 1 twenty-four hours before the virus was injected. Area 2 is the untreated (control) area of skin. Xylene was applied to area 3 immediately after intravenous injection of 5 cc. of a saline suspension of vaccine virus. The photograph was made on the seventh day after injection of the virus. At this time there were nine lesions in area 1, five in area 2 and thirty in area 3.

separated by centrifugation. One to 5 cc. of this virus suspension was injected into the marginal veins of the ear. Xylene was applied to one area of skin twenty-four hours before the virus was injected and to another area of skin in the same animal immediately after injection of the virus. An area of skin of equal size was outlined for the control.

The number of vaccinal lesions that appeared in both the xylene-treated and the untreated areas of skin varied with the different rabbits. The greatest number of vaccinal lesions, however, always occurred in the area of skin where xylene was applied immediately after intravenous injection of the virus.

Approximately an equal number of lesions occurred in the normal skin and in those areas of skin treated with xylene twenty-four hours prior to intravenous injection of the virus. Figure 3 shows the vaccinal lesions in the two xylene-treated areas and in the normal skin. Xylene was applied over area 1 twenty-four hours before the animal was given the suspension of virus intravenously; area 2

is normal skin. Xylene was applied over area 3 immediately after injection of the virus. Seven days after injection of the virus there were nine lesions in area 1, five in area 2 and thirty in area 3.

Two rabbits in this group showed almost a confluent vaccinal lesion in the untreated skin over the back and only a few isolated lesions on the lower portion of the abdomen. The hair subsequently grew much more quickly over the backs of these rabbits than along the lower part of the abdomen. Two other rabbits showed focal collections of vaccinal lesions in areas where the hair was growing rapidly in both the xylene-treated and the untreated areas of skin.

COMMENT

This series of observations shows that trypan blue, carbon particles, antitoxin and vaccine virus when injected into the circulating blood concentrate in areas of inflammation produced by xylene only during a specific interval. The time in which these substances localize and concentrate in the xylene-treated areas of skin is not determined by the presence or absence of edema, hyperemia and leukocytic infiltration of the skin. In fact, there is little edema or hyperemia at the time trypan blue localizes in those areas of skin where xylene is placed immediately before the dye is injected. Furthermore, there may be all the macroscopic and microscopic changes commonly associated with inflammation, and still the dye may not concentrate.

It is interesting that substances varying as widely as those used in this study all localize relatively the same with regard to the time of application of xylene and the intravenous injection of the substances. This observation suggests that the capillaries become more permeable immediately after application of xylene and then gradually return to their normal state of permeability. Apparently the capillaries require approximately three hours after application of xylene to return to their normal state of permeability. At this time the skin may be edematous and hyperemic, and leukocytes may be infiltrating the area.

Foreign substances (those used in this experiment and many others) have frequently been found to localize and concentrate in areas of inflammation.[5] Hanger [1b] observed that after an intravenous injection carbon particles did not always localize in areas of inflammation. There is a definite period in which these particles localize in the skin after intradermal injection of a filtrate of Bacillus lepisepticus. The localization is explained on the basis of phagocytosis of the carbon particles by the capillary endothelium. Fox [5a] likewise observed a definite period in which trypan blue, hemolysins and agglutinins after intravenous

5. (*a*) Fox, J. P.: The Localization and Concentration of Blood Borne Antibodies and Colloidal Dye in Areas of Inflammation of Various Ages, J. Immunol. **31**:283-308, 1936. (*b*) Berlin, M.: Antitoxine tétanique et abscès de fixation, Compt. rend. Soc. de biol. **102**:731-733, 1929. (*c*) Footnote 1.

injection would concentrate in areas of inflammation. The failure of these substances to concentrate in an area of inflammation was explained by Fox on the basis of thrombotic occlusions. In the discussion of his work he stated: "The demonstration of the relationship between the stage of inflammation and the ability of an inflammatory process to localize blood-borne materials is important for its bearing on clinical problems, and also in clarifying the concepts of Menkin[6] and Burrows.[2] Such a qualification of this newly emphasized attribute of inflammation may seem rather obvious, yet, as we have seen, neither of the above authors has given the matter adequate experimental consideration."

Irritants other than xylene have been used in this study of the localization of trypan blue in areas of inflammation. Trypan blue will localize and concentrate in areas of skin where staphylococcus toxin is injected intradermally provided the dye is given intravenously within thirteen hours after injection of the toxin. This colloidal dye when given intravenously will also localize in an area of the rabbit's skin where horse serum has been injected twenty-four hours previously. The greatest amount of dye localizes in the area of skin where the horse serum is injected immediately before the dye. Trypan blue in these experiments has not been observed to localize and to concentrate in areas of inflammation produced by the intradermal injection of infusion broth cultures of staphylococci when given intradermally eight and twenty-four hours previously. This dye when given intravenously also does not concentrate in areas of the skin where 1.0 cc. of a 1 per cent solution of sodium chloride is injected intradermally. It does localize and concentrate, however, in those areas of the skin treated with a similar quantity of a 4 per cent sodium chloride solution, even in the same rabbit. Trypan blue fails to concentrate in the areas of skin when it is given intravenously sixty minutes after intradermal injection of this hypertonic salt solution.

Trypan blue is always retained for a much longer time in tissues which show inflammatory changes than in the normal skin. This study illustrated the importance of clearly differentiating localization and concentration from fixation or retention of trypan blue in inflammatory tissue. The former may occur in areas where there is no cellular evidence of inflammation; the latter occurs only in the areas that show such a reaction. The difference between localization and concentration of a dye and retention can be determined macroscopically by observing the tissue immediately after intravenous injection of the dye.

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6. Menkin, V.: An Aspect of Inflammation in Relation to Immunity, Arch. Path. **12**:802-828 (Nov.) 1931; A Note on the Mechanism of Fixation in an Area of Sterile Inflammation, Proc. Soc. Exper. Biol. & Med. **30**:1069-1076, 1933.

A knowledge of the relation between increased capillary permeability and the diapedesis of leukocytes is important in any consideration of inflammation and immunity. A consideration of the mechanism of capillary permeability based on experimental studies will be subsequently reported.

SUMMARY

The capillaries in the skin of the rabbit show an increase in permeability for approximately three hours after local application of xylene. This is indicated by the localization of trypan blue, india ink, antitoxins and vaccines virus in such areas. The skin may show all the cardinal features of inflammation, and still these substances may fail to localize and concentrate in the tissue. The period for which capillaries are more permeable may vary with different irritants. This is shown by the fact that trypan blue when given intravenously localizes and concentrates in areas of skin into which a 4 per cent sodium chloride solution was injected intradermally sixty minutes prior to injection of the dye. This same dye localizes and concentrates in the skin of the rabbit where horse serum is injected intradermally when the latter is given as long as twenty-four hours prior to intravenous injection of the dye.

The staphylococcus antitoxin used in this study was supplied by the Lederle Laboratories.

RESECTION OF THE CARCINOMATOUS RECTO-SIGMOID JUNCTURE WITH REESTABLISHMENT OF INTESTINAL CONTINUITY

SUBSEQUENT REPORT

HUBERT R. ARNOLD, M.D.
AND
J. FRANK SHEA, M.D.
SAN FRANCISCO

Since publication of the original article on this subject by one of us (H. R. A.), we have performed four more such operations, bringing the total to 5.

The reader is referred to the original article [1] for technic and illustrations of the procedure.

The second, third and fourth operations were carried out exactly as was originally described.[1] The second patient was operated on in December 1937. She was 68 years of age and well nourished. Her recovery was uneventful, and today she is well, with a normal anus, normal control of the bowel and no sign of recurrence. The third patient was a man 77 years of age and a poor surgical risk. He died on the tenth postoperative day as a result of gangrene of the distal portion of the sigmoid flexure with diffuse peritonitis. Gangrene was due to thrombosis of the blood supply to the distal portion of the sigmoid flexures, as was shown by autopsy. The fourth patient was operated on in June 1939. She made an uneventful recovery.

By further study of the blood supply we decided that the superior hemorrhoidal artery should be ligated at a point below the lowermost sigmoid branches, since the portion of the sigmoid flexure remaining would be amply supplied by the sigmoid branches, and the part of the bowel supplied by the superior hemorrhoidal artery would be resected (fig. 1). By this means it would not be necessary to search for the so-called "critical point," and the sigmoid arterial branches would not be traumatized and therefore predisposed to thrombosis. In this manner the sigmoid arch of the blood vessels would not have to be preserved, since the sigmoid branches would be left intact above the point of ligation of the superior hemorrhoidal artery. The sigmoid arteries supply the sigmoid flexure to the rectosigmoid juncture, and the sigmoid flexure is amputated 2 to 4 inches (5 to 10 cm.) above this point, together with

1. Arnold, H. R.: Resection of the Carcinomatous Rectosigmoid Juncture, Arch. Surg. **38**:1004-1013 (June) 1939.

a large triangle of the mesocolon. Naturally, the middle hemorrhoidal arteries running in the lateral bands of the rectum are severed when this structure is cut. The inferior hemorrhoidal arteries by their anastomoses supply the stump of the rectum left after the portion of

Fig. 1.—Illustration from Deaver's "Surgical Anatomy" (Philadelphia, P. Blakiston's Son & Co., 1901, vol. 1). *X* indicates the point at which the superior hemorrhoidal artery is ligated below the sigmoid arteries.

bowel containing the rectosigmoid juncture with the tumor is removed. Of course, in some instances, as is shown in figure 2, it would be easy to ligate the superior hemorrhoidal artery above the lowermost sigmoid branch, which forms the sigmoid arch, above the so-called critical point of Hartmann.

REPORT OF MOST RECENT CASE

The fifth and last patient operated on was treated by ligating the superior hemorrhoidal artery at a point below the lowermost sigmoid branches. He was a man 68 years of age and a very good surgical risk.

He was operated on Aug. 18, 1939. His course was uneventful to the eighth postoperative day, when the upper part of the incision broke open. He was given 150 mg. of procaine hydrochloride intraspinally, and the incision was cleaned. The bowels were distended, and therefore a cecostomy was done to decompress them. The abdomen was then closed without difficulty with retention sutures of silkworm gut and heavy chromic sutures. The wound healed per primam intentionem, and cecostomy worked excellently.

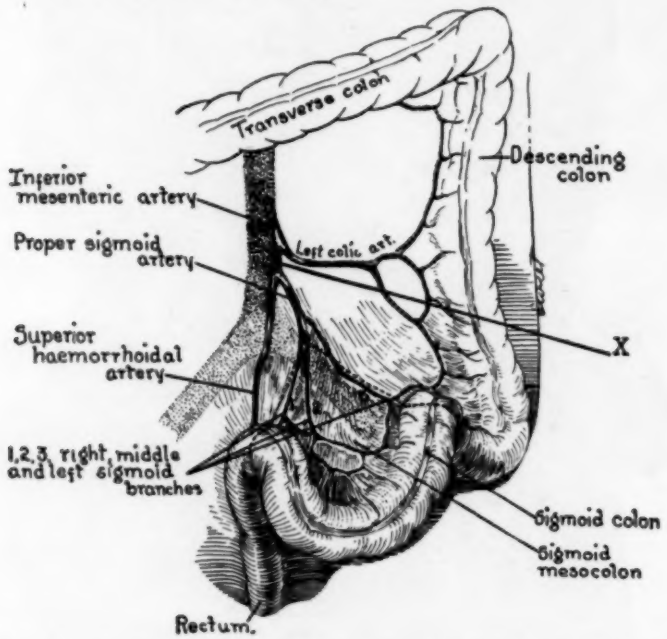

Fig. 2.—Sigmoid flexure of the colon and mesocolon, with special reference to the arterial supply. The arteries to the sigmoid flexure are the left (*3*), middle (*2*) and right (*1*) sigmoid arteries, which are branches from the inferior mesenteric artery; the large single branch of the inferior mesenteric artery is the superior hemorrhoidal artery, which supplies the upper part of the rectum. *X* indicates the point of ligation. Illustration from Callander's "Surgical Anatomy" (Philadelphia, W. B. Saunders Company, 1933).

Figure 3 shows the specimen removed at operation. Microscopic sections showed no metastatic nodules.

On the twelfth day after the original operation, clamps were applied to the septum in the double-barreled sacral colostomy, and these came off on the fourth day.

(It cannot be emphasized too strongly that the septum should be cut down to a depth of approximately 5 inches (12.7 cm.). The usual right angle clamps have

too short a blade to crush the septum to this depth. When the first clamp sloughs out, it should be reapplied to crush the remainder of the septum if the septum has not been completely disposed of with the first crushing.)

The sacral colostomy opening closed spontaneously by November 15, and the cecostomy stoma was closed surgically with the region under local anesthesia two weeks later.

The rapid closing of the sacral colostomy stoma in this case was undoubtedly due to the presence of the cecostomy opening. However,

Fig. 3 (case 5).—Specimen of the rectosigmoid juncture.

the cecum should not be opened until the primary abdominal wound has been allowed to heal for several days.

There has been a heated debate in the literature over the spread of carcinoma in the distal part of the sigmoid flexure and in the rectosigmoid juncture. The consensus at present is that downward spread is late and insignificant. Any one interested is referred to the voluminous literature on this subject. The operation described is not applicable to carcinoma of the rectal ampulla, nor is it applicable to inoperable carcinoma in or above the rectosigmoid juncture. It is hoped that by use of this procedure in cases of early operable carcinoma in this region patients will be given the benefit of normal control instead of an abdominal colostomy.

EVALUATION OF THE INJECTION TREATMENT OF HERNIA IN OLDER PATIENTS

A THREE YEAR STATISTICAL ANALYSIS

LAZARUS MANOIL, M.D.
NEW YORK

The purpose of this paper is to present a brief analysis of cases of hernia treated by the injection method and to indicate the type of case in which this method of treatment is preferable. The consensus among surgeons is that operative measures are the best method of treating hernia. However, the management of older patients is always a problem, especially when another disease coexists. The high percentage of postoperative recurrence in such a group, due to a variety of causes, such as poor wound healing, infections and other complications, invites investigation of less hazardous procedures which promise relief. There is also a large group of younger patients who refuse operation because of fear, because of inability to meet the economic burden incurred or because they are unwilling to take "time off" for the operation. It is with these groups in mind, particularly the first, that study of the efficacy of the injection treatment was undertaken. Needless to say, this method has been enthusiastically recommended by many investigators.

The rationale of this method is to stimulate a high degree of fibroblastic proliferation firmly rooted in the surrounding defective muscle and fascia with as little inflammatory reaction as possible. If sufficient scar tissue can be produced to constrict the internal and external inguinal rings and partially obliterate the inguinal canal or its fascial plane, the end result may be similar to that obtained by operation except for removal of the sac. With the injection method, the sac remains empty, functionless and compressed by the surrounding proliferation of fibrous tissue. Therefore, not only is it unnecessary to obliterate the sac, but it is extremely dangerous to inject the sclerosing solution into it, because of the chemical peritonitis that will result. Healthy proliferation of scar tissue without pain or toxic effects was successfully produced with sylnasol (a 5 per cent solution of the sodium salts of certain of the fatty acids of the oil

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From the Hernia Clinic, the Surgical Service of Dr. J. Girsdansky, Gouverneur Hospital.

extracted from a seed of the psyllium group). This has been demonstrated previously by a comparative histologic study of tissue response to other sclerosing solutions.[1]

In addition to a safe and effective sclerosing solution, the use of a well fitting truss is essential. It must be worn day and night during the course of injections, which takes six to eight weeks if given two or three times a week. Thereafter the patient may remove the truss at night but must wear it during the day for four to six months. My associates and I have used bilateral frame trusses in most of the cases reported in this series. Since completion of this study, in February 1939, we have been prescribing only semielastic trusses. These are more comfortable for steady wear; they hold the hernia reduced properly, and they cause little or no irritation of the skin, such as has occasionally occurred with the frame truss. Continuous pressure to keep the hernia reduced during the course of treatment is very important; without it serious complications may result. It is equally important that the patient cooperate in wearing the truss as instructed. Two patients in our series were operated on for strangulation of the hernia because they removed their trusses at home against advice.

The injection treatment of hernia, in my opinion, is particularly indicated for older patients who are considered poor surgical risks because of their age, their state of nutrition or other coexisting conditions. It is also indicated for younger patients who refuse operation but are willing to cooperate in this treatment even though it is prolonged. The best result may be expected in the case of a small inguinal hernia, but our series includes not only large indirect inguinal but direct inguinal, postoperative recurrent inguinal, scrotal, femoral, umbilical and postoperative ventral types. Most of these were of many years' duration. All of them can be helped provided they are completely reducible and can be kept reduced with comfort during the course of treatment. The patient is ambulatory, and the treatment does not interfere with his means of livelihood and other activities.

The chief contraindication is an irreducible hernia. This condition is very dangerous to treat by injections. Patients who do not cooperate or cannot be fitted comfortably with a truss should not be treated by this method. Sliding hernia and undescended testicles should be considered contraindicative. Diabetes, syphilis, chronic bronchitis, asthma, tuberculosis, prostatic disease and cardiac disorders are also considered contraindications by most observers, but in the hernia clinic we have not found them contraindicative.

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1. Manoil, L.: Histologic Effects of Various Sclerosing Solutions Used in the Injection Treatment of Hernia, Arch. Surg. **36**:171-189 (Feb.) 1938.

STATISTICAL STUDY

The data in the following tables are based on the study of 608 patients observed between February 1936 and February 1939. In 123 of these, 158 hernias were treated.

Table 1 shows the results in the cases in which the injection method was used. We arbitrarily considered as cured only those patients who continued to be symptomless without a truss for over six months after treatment. The period of treatment included the series of injections and a subsequent four to six month interval of truss support. In this group there were 19 hernias (12 per cent).

Patients who continued to wear their trusses six months after completion of treatment but who had no signs or symptoms of hernia were grouped as possibly cured. In this group there were 20 hernias (12.7 per cent).

TABLE 1.—*Results of Injection Method*

Group A1 (cured without truss for over 6 months after treatment)	19, or 12 %
Group A2 (possibly cured but still wearing truss 6 months after treatment)	20, or 12.7%
Group A3 (possibly cured and still wearing truss less than 6 months after treatment)	26, or 16.4%
Group A4 (possibly cured but not seen after 1 year of observation)	14, or 8.9%
Group B (clinically improved but not cured; includes those still under treatment)	48, or 30.4%
Group C (recurrences and failures)	26, or 16.4%
Group D (operated on after injection treatment)	5, or 3.2%
Total number of hernias	158

Patients who had no signs or symptoms of hernia and were still wearing their trusses less than six months after completion of treatment were grouped separately. In this group there were 26 hernias (16.4 per cent).

There was also a smaller group of patients without symptoms, some of whom discarded their trusses, while others continued to wear them but failed to reappear for examination after one year of observation. In this group there were 14 hernias (8.9 per cent).

In this table is included also a group of patients who after an adequate course of treatment still showed a slight impulse or slight bulging on straining but who were completely relieved of their subjective symptoms. These patients were definitely improved. Most of them continued to wear their trusses during the day. This group also included those still under treatment. In this group there were 48 hernias (30.4 per cent).

Recurrences and failures occurred with 26 hernias (16.4 per cent). The group represented by these includes patients who were clinically cured but who subsequently showed complete or partial recurrence. Many of these returned for continuation of injections. There was 1

patient whose hernia recurred three times after clinical cure by injection. There were 3 patients each of whom had two recurrences after treatment. In many of these cases recurrence or failure was unquestionably due to a poorly fitting or improperly worn truss, insufficient treatment or poor wound healing. This group also included patients who received more than six injections but did not complete the course of treatment.

Five patients (3.2 per cent) were operated on after the injection treatment; 2 because the hernia strangulated, 2 because the hernia recurred after injections and 1 because of impatience and dislike of the needle. There were no special difficulties at operation because of former injections.

TABLE 2.—*Analysis of Patients Seen But Not Treated*

Waiting for trusses	33
Refusing any kind of treatment	35
Unable to get trusses	6
Unable to fit with trusses	3
Not cooperative	2
Not suitable for treatment	17
Did not return for treatment after given truss	221
Operation advised	96
No hernia found	37
"Compensation cases"	9
Not examined	5
Treated with adhesive strapping	1
Total	465

TABLE 3.—*Types of Hernia Treated*

Indirect inguinal	68, or 43 %
Direct inguinal	45, or 28.5%
Recurrent inguinal	17, or 10.8%
Scrotal	22, or 14 %
Femoral	3, or 1.9%
Umbilical	1, or .6%
Postoperative ventral	2, or 1.2%
Bilateral inguinal	42, or 34.1%
Total	158

In table 2 are classified the large group of 465 patients who were seen at the clinic but were not given injection treatments. It is interesting to note that 221 patients in this group desired only the mechanical support of a truss, refusing operation or injection. Ninety-six younger patients were referred for operation.

Table 3 shows the types of hernia treated. Most of the hernias were large, and some had existed from forty to sixty years. Sixty-eight (43 per cent) were indirect inguinal, 45 (28.5 per cent) were direct inguinal and 17 (10.8 per cent) were recurrent inguinal hernias. Four of these were bilateral and recurrent; several had been operated on twice, with recurrence, and 1 had been operated on three times, with recurrence.

There were also 22 scrotal hernias (14 per cent) of many years' duration. One patient had a bilateral femoral and 1 a recurrent femoral hernia. There was 1 female patient with an umbilical hernia 3 cm. in

TABLE 4.—*Analysis of Types of Hernia Classified in the Results of Each Group Treated*

Group A1 (cured without truss for over 6 months after treatment)		
	11	Indirect inguinal
	4	Direct inguinal
	1	Recurrent inguinal
	2	Scrotal
	1	Postoperative ventral
	19	
Group A2 (possibly cured but still wearing truss 6 months after treatment)		
	8	Indirect inguinal
	5	Direct inguinal
	5	Recurrent inguinal
	2	Scrotal
	20	
Group A3 (possibly cured less than 6 months after treatment and still wearing truss)		
	7	Indirect inguinal
	8	Direct inguinal
	2	Recurrent
	6	Scrotal
	2	Femoral
	1	Umbilical
	26	
Group A4 (possibly cured but not seen after 1 year of observation)		
	6	Indirect inguinal
	5	Direct inguinal
	3	Scrotal
	14	
Group B (clinically improved but not cured)		
	20	Indirect inguinal
	14	Direct inguinal
	6	Recurrent inguinal
	7	Scrotal
	1	Postoperative ventral
	48	
Group C (recurrences and failures)		
	13	Indirect inguinal
	8	Direct inguinal
	3	Recurrent inguinal
	2	Scrotal
	26	
Group D (operation after injection treatment)		
	3	Indirect inguinal
	1	Direct inguinal
	1	Femoral
	5	

diameter that was completely closed after 5 injections. Of the 2 postoperative ventral hernias, 1 followed a suprapubic prostatectomy and the other an appendectomy through a McBurney incision. It is interesting to note that there were 42 bilateral inguinal hernias (34.1 per cent) in this series of cases.

Table 5 shows the number of patients operated on in each group and the number of recurrences and failures in cases of hernia treated by injection. The incidence of recurrence and failure was about the same for indirect, direct and recurrent inguinal hernia. The percentage of failures for scrotal hernia was about half of those noted for the aforementioned types. Three indirect inguinal hernias, 1 direct inguinal hernia and 1 femoral hernia were operated on in this whole series.

Table 6 shows the percentage of recurrence in each age group. It is interesting to note here that 108 patients, or 92 per cent of the entire

TABLE 5.—*Classification of Recurrences and Failures and Cases in Which Operation Was Performed for Each Type of Hernia*

Number of Hernias	Number and Per Cent of Recurrences and Failures	Number and Per Cent of Patients Operated On
68 indirect	13, or 19.1	3, or 4.4
45 direct	8, or 17.8	1, or 2.2
17 recurrent	3, or 17.7	0 0
22 scrotal	2, or 9.1	0 0
3 femoral	0 0	1, or 33.3
1 umbilical	0 0	0 0
2 postoperative	0 0	0 0

TABLE 6.—*Analysis of Recurrence Rate in Each Age Group*

Age	Number of Patients	Number of Hernias	Recurrences	Per Cent
11-20	1	1	0	0
21-30	2	3	0	0
31-40	12	13	0	0
41-50	24	34	7	20.5
51-60	36	47	12	25.5
61-70	36	45	4	8.9
71-80	11	14	3	21.4
81-90	1	1	0	0

series, were between 41 and 90 years of age. There were 7 recurrences (20.5 per cent) among the 34 hernias in patients of the age group between 41 and 50. There were 12 recurrences (25.5 per cent) among the 47 hernias in patients of the age group from 51 to 60. There were 4 recurrences (8.9 per cent) among the 45 hernias in patients of the age group from 61 to 70. Lastly, there were 3 recurrences and failures (21.4 per cent) among 14 hernias in the patients between 71 and 80 years of age.

Table 7 shows the relation of the patient's age to the results of treatment. In the younger group of patients (between 11 and 40 years of age) there were no recurrences. Six after removal of the truss remained cured; 3 who were still wearing their trusses over six months after completion of treatment continued to be symptomless; 1 was pos-

sibly cured but was within the six month period since completion of treatment; 2 were possibly cured but were not seen after one year of observation following completion of treatment, and 4 were clinically improved or still under treatment. In the older group of patients between 41 and 90 years of age, there were 26 recurrences and failures (16.4 per cent), while 5 (3.2 per cent) were operated on. This totals 19.6 per cent of failures. Thirteen patients were cured and without truss support over six months after completion of treatment; 17 were still wearing their trusses over six months after completion of treatment but continued to be symptomless; 25 were possibly cured but were within the six month period since completion of treatment; 12 were possibly cured but were not seen after one year of observation following completion of treatment, and 43 were clinically improved or still under treatment.

TABLE 7.—*Analysis of Results in Relation to Age of Patients*

	Group *						
Age	A1	A2	A3	A4	B	C	D
11-20	1	0	0	0	0	0	0
21-30	2	0	0	0	1	0	0
31-40	3	3	1	2	4	0	0
41-50	4	7	6	3	6	7	1
51-60	3	5	5	4	15	12	4
61-70	4	5	10	4	17	4	0
71-80	2	0	4	1	4	3	0
81-90	0	0	0	0	1	0	0
	19(12%)	20(12.7%)	26(16.4%)	14(8.9%)	48(30.4%)	26(16.4%)	5(3.2%)

* For explanation of groups, see table 1.

Complications were comparatively few during the last eighteen months of the study, owing to improvement of technic. Altogether, during the entire three year period, there were eight swellings of the cord, which subsided in two or three weeks, and twenty-two peritoneal reactions characterized by local or general abdominal pain. These reactions usually cleared up within one to three hours. There were 2 cases of strangulation, as has been noted. No cases of atrophy of the testes or sexual impotence were noted. There were no infections and no mortalities.

COMMENT

The reports in the literature in the past ten years on the injection treatment of hernia, by Fowler,[2] Rice [3] and Bratrud [4] of the Minneapolis

2. Fowler, S. W.: Experience with the Injection Treatment of Hernia, M. Rec. **101**:207-209 (Feb. 20) 1935.

3. Rice, C. O.: The Injection Treatment of Hernia: Evaluation of Technic and Results, Ann. Surg. **105**:343-351 (March) 1937.

4. Bratrud, A. F.: Ambulant Treatment of Hernia, Journal-Lancet **54**:337-341 (June 15) 1934.

General Hospital, McKinney [5] of the University of Minnesota, McMillan and Cunningham [6] from the department of surgery of the Northwestern Medical School, Crohn [7] of the Michael Reese Hospital, Chicago, Harris and White [8] of San Francisco and many others, show invariably a high percentage of cures in well selected cases of hernia treated by the injection method. The only report of extremely discouraging results made after a two year study of only 66 cases was that of Burdick and Coley [9] of the Hospital for the Ruptured and Crippled, New York. From a three year statistical study of 123 patients with 158 hernias, my associates and I were convinced that the results do not indicate a large percentage of cures but do indicate an excellent palliative result in a large number of cases. It must be borne in mind that 92 per cent of the patients treated were between 41 and 90 years of age with large hernias of long duration, many of whom would have been considered poor surgical risks. There is no doubt that many of these patients would have continued to be uncomfortable with or without a truss if they had not been given the injection treatment. Most of them have been satisfied with the result, and many have been able to return to some type of work. Patients with recurrence after injection treatment were given a subsequent series of injections to secure firm closure of the hernia. The hernias that failed to close improved sufficiently to enable the patient to wear a truss comfortably and to maintain the hernia in complete reduction. In the small group of 15 younger patients (between the ages of 11 and 40) no recurrences have been noted to date. One might infer from this that the injection method compares favorably with operation for younger patients. I reiterate that the injection method is the method of choice for older patients, for reasons already mentioned.

Wangensteen [10] stated:

> It is not without significance that not one patient of several hundred treated by the injection method in the 2 surgical clinics (U. of Minnesota, and Minneapolis General Hospital) has died as a direct result of this treatment. As much can

5. McKinney, F. S.: An Evaluation of the Results of the Injection Treatment of Inguinal Hernia: Review of Employment of This Method at University of Minnesota Hospital, Ann. Surg. **105**:338-343 (March) 1937.

6. McMillan, W. M., and Cunningham, D. R.: The Injection Treatment of Reducible Hernia, J. A. M. A. **106**:1791-1795 (May 23) 1936.

7. Crohn, N. N.: The Injection Treatment of Hernia, J. A. M. A. **108**:540-544 (Feb. 13) 1937.

8. Harris, F. I., and White, A. S.: Evaluation of the Injection Treatment of Hernia, J. A. M. A. **111**:2009-2013 (Nov. 26) 1938.

9. Burdick, C. G., and Coley, B. L.: Injection Method of Treating Hernia, Ann. Surg. **106**:322-333 (Sept.) 1937.

10. Wangensteen, O. H.: The Status of the Injection Treatment of Hernia, Ann. Surg. **105**:322-324 (March) 1937.

rarely be said for large series of similar size treated by operation. This method of treating selected cases of hernia has merit and when skillfully employed would appear to carry little risk of serious complication.

He continued:

Medicine has come to recognize the superiority of trial over reason. Rationalizations concerning the merits of a method are likely to lead to error, not so much because the logic employed is poor but more often because the initial premise itself is false. The injection treatment of hernia is not therefore to be dismissed without examination. The rejection of obliteration of hemorrhoidal varicosities and varicose veins of the lower extremities by injection is fresh enough in the recollection of medical men to remind them that the prejudices cannot delay the march of progress.

SUMMARY AND CONCLUSIONS

The injection method of treating hernia has many advocates. Many clinics here and abroad have been giving it ever increasing attention. The importance of the principles to be observed in the management of hernia as originally stated by Billroth, and affirmed more recently by Bratrud, Rice, Wangensteen and others, cannot be overemphasized. These principles are the use of a safe and effective sclerosing solution, a satisfactory truss, knowledge of the regional anatomy and full cooperation of the patient.

During the period between February 1936 and February 1939, 158 hernias in 123 patients were treated by the injection method at this clinic. Ninety-two per cent of these patients were between 41 and 90 years of age. Recurrence took place in 26, or 16.4 per cent, of this group, and 5 patients, or 3.2 per cent, were operated on after injection, making a total percentage of failures of 19.6 per cent. In the 15 younger patients between 11 and 40 years of age there were no recurrences. There were no infections and no mortality. The injection treatment is the method of choice for older patients provided the hernia is reducible and can be comfortably maintained with a truss. It should be the alternative method of treatment for younger patients who refuse operation.

PATHOLOGY OF SHOCK IN MAN

VISCERAL EFFECTS OF TRAUMA, HEMORRHAGE, BURNS AND SURGICAL OPERATIONS

HARRY A. DAVIS, M.D.
NEW ORLEANS

Present knowledge of the syndrome of shock in man rests largely on physiologic investigations in lower animals. Studies of pathologic changes are decidedly more limited, and Moon and Kennedy [1] deserve much credit for drawing attention to the importance of these alterations.

The present study is concerned with the visceral changes present in 50 patients who died in a state clinically diagnosed as shock and on whom postmortem examinations were performed from one to three hours later. An effort has been made to demonstrate that definite alterations occur in the viscera as the result of shock and that the character of these changes is dependent on the etiologic factors involved. The changes are grouped according to the clinical states from which they arose, and their significance is briefly discussed. These states include:

1. Cerebral trauma—10 cases
   - A. Early death
   - B. Delayed death
2. Trauma to the abdomen, thorax or extremities—31 cases
   - A. Early death with
     - (*a*) Open hemorrhage
     - (*b*) Closed hemorrhage
     - (*c*) Regional segregation of blood
     - (*d*) Infection
   - B. Delayed death
3. Trauma following burns—5 cases
   - A. Early death
   - B. Delayed death
4. Trauma following surgical procedures—4 cases

From the Department of Pathology of the University of Tennessee School of Medicine and the Department of Surgery of the School of Medicine of Louisiana State University.

1. Moon, V. H., and Kennedy, P. J.: Pathology of Shock, Arch. Path. **14:** 360-371 (Sept.) 1932.

CEREBRAL TRAUMA

In this group of 10 cases trauma resulted either from a gunshot wound or from direct contusion with a blunt instrument. In the majority of instances death occurred within eighteen hours and was most rapid after gunshot injuries.

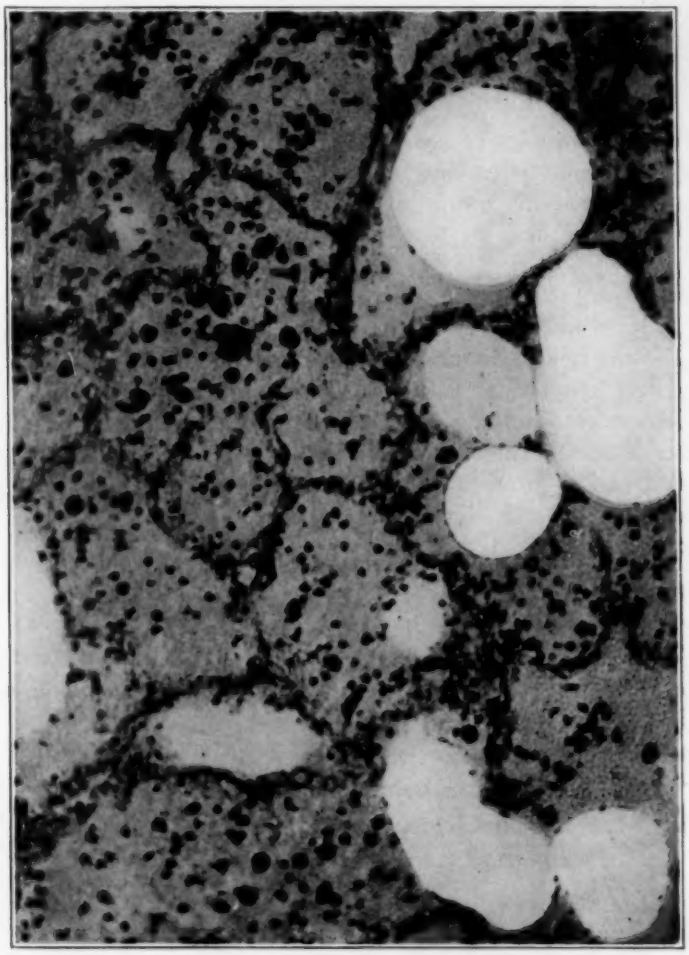

Fig. 1.—Lung (× 210) from a case of cerebral trauma with early death. Note pulmonary edema, congestion of the alveolar capillaries and diapedesis of erythrocytes into the alveoli. Many "heart failure" cells are present.

In fatal cases of cerebral trauma there is present a dilatation which is probably generalized in character but which is manifested at autopsy chiefly as a vascular congestion of the lungs and the abdominal viscera. This dilatation would seem to be dependent on failure of the vasomotor

center, which in turn follows prolonged oxygen deficiency. Edema of the lungs, with diapedesis of red blood cells into the alveolar spaces, and numerous macrophage cells containing iron pigment are also more or less constant findings (fig. 1).

It should be pointed out that it is impossible to exclude as a factor in the production of the pathologic picture the effect of cardiac failure

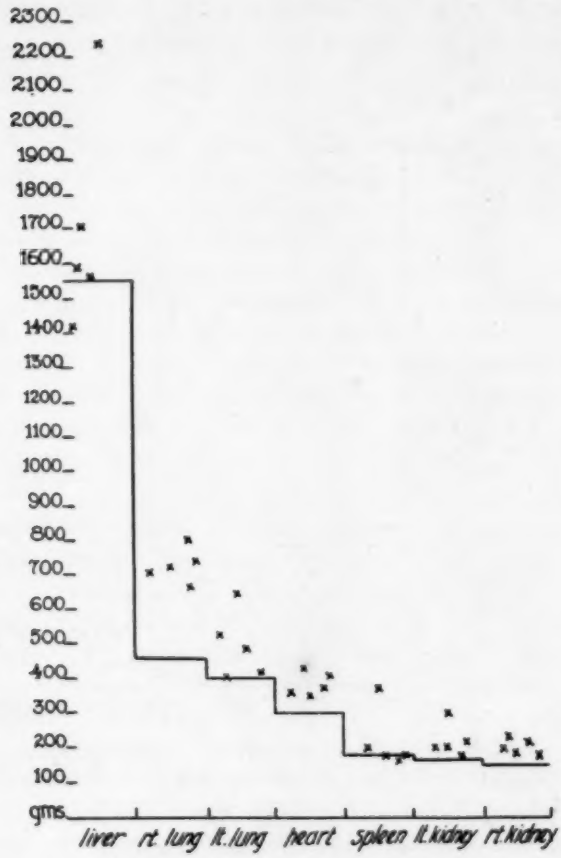

Fig. 2.—Distribution of visceral weights in 5 cases of cerebral trauma with early death.

with progressive diminution of the cardiac output. It is suggested that any condition which leads to anoxemia of the central nervous system would seem to be capable of producing similar pathologic changes. It is also suggested that the pathologic picture is necessarily dependent on the total circulating blood volume at the time of death. Reduction of the blood volume, whether by open or by closed hemorrhage, tends to obscure the presence of a terminal vasodilatation. The presence of

pulmonary edema even in patients to whom fluids have not been administered intravenously suggests that an altered permeability of the pulmonary capillaries occurs.

A study of the viscera in this group of patients revealed a definite increase in weight due to the distention of the blood vessels with blood (fig. 2).

The available facts would seem to point, therefore, toward two processes at work in the production of the visceral pathologic changes fol-

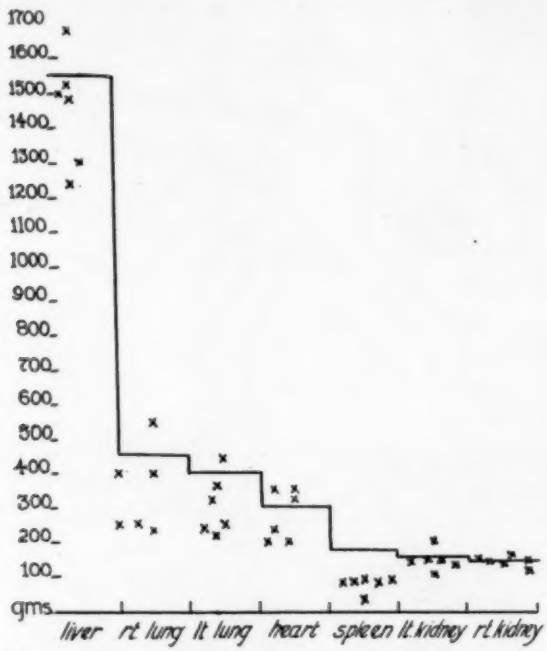

Fig. 3.—Distribution of visceral weights in 6 cases of trauma to the abdomen, thorax or extremities with open hemorrhage and early death.

lowing cerebral trauma: (1) a vasodilatation in the splanchnic and thoracic areas and (2) cardiac failure. The time factor is of great importance here. When cerebral compression occurs very rapidly and death also occurs quickly, extreme thoracic and splanchnic vasodilatation is found. When cerebral compression is more gradual and death slower, the central vasodilatation, although still present, is less marked. A similar type of vasodilatation has been produced experimentally in dogs by either rapid or gradual increase in intracranial pressure (Davis [2]). It has also been reported following cerebral edema (Ala-

2. Davis, H. A.: Unpublished data.

jouanine and Hornet [3]) and traumatic lesions of the brain stem (Wanke [4]). Blalock [5] has pointed out that in experimental cerebral trauma a diminution of cardiac output occurs simultaneously with a reduction in blood pressure.

TRAUMA TO THE THORAX, ABDOMEN OR EXTREMITIES

Before discussing the group of 31 cases in which death occurred promptly after trauma to the abdomen, thorax or extremities, it is necessary to define the terms "open hemorrhage" and "closed hemorrhage." In the sense intended here, the term "open hemorrhage" means free hemorrhage into an open cavity, such as the peritoneal or pleural cavities, or external bleeding. Closed hemorrhage signifies hemorrhage into tissues which prevent its escape externally or into an open cavity. Retroperitoneal hemorrhage, intramesenteric hemorrhage and intramuscular hemorrhage are all instances of the closed variety. The distinction between open and closed hemorrhage is of great importance in the interpretation of the pathologic changes in shock in relation to the administration of fluids. Those cases in which death occurred within forty-eight hours of the receipt of the injury were grouped as early deaths. Those in which death occurred after forty-eight hours were considered as delayed deaths. This grouping is entirely arbitrary.

Early Death from Open Hemorrhage.—To speak generally, in this group of cases the amount of free blood varied from 900 to 2,200 cc. The heart revealed no pathologic change other than marked contraction. The spleen was also markedly contracted. The liver was usually pale and anemic, and the weight was normal or subnormal. The liver cells were usually swollen, and the liver capillaries were empty. The kidneys had a tendency to be reduced in weight and usually were pale and dry in appearance. The epithelium of the convoluted tubules showed varying degrees of parenchymatous degeneration. The visceral weights were decreased (fig. 3).

The changes in the lungs were interesting. The weight, as a rule, was below normal, but the longer the duration of the shock the heavier were the lungs. The color was pale, and there was no evidence of petechial hemorrhages. Varying degrees of emphysema were observed on microscopic examination. There was moderate congestion of the alveolar capillaries, with moderately frequent collections of "heart

3. Alajouanine, T., and Hornet, T.: L'oedème cérébral generalisé (étude anatomique), Ann. d'anat. path. **16**:133-163 (Feb.) 1939.

4. Wanke, R.: Zum Nachweis und zur Auswirkung der traumatischen Hirnstammläsion, Arch. f. klin. Chir. **193**:676-701, 1938.

5. Blalock, A., and Bradburn, H. B.: Trauma to Central Nervous System: Its Effects on Cardiac Output and Blood Pressure; Experimental Study, Arch. Surg. **19**:725-734 (Oct.) 1929.

failure" cells (fig. 4.) Pulmonary edema was not usually present, particularly in those patients who died within twelve to eighteen hours after admission to the hospital. When present, it was patchy in character. No diapedesis of red blood cells into the alveolar spaces was

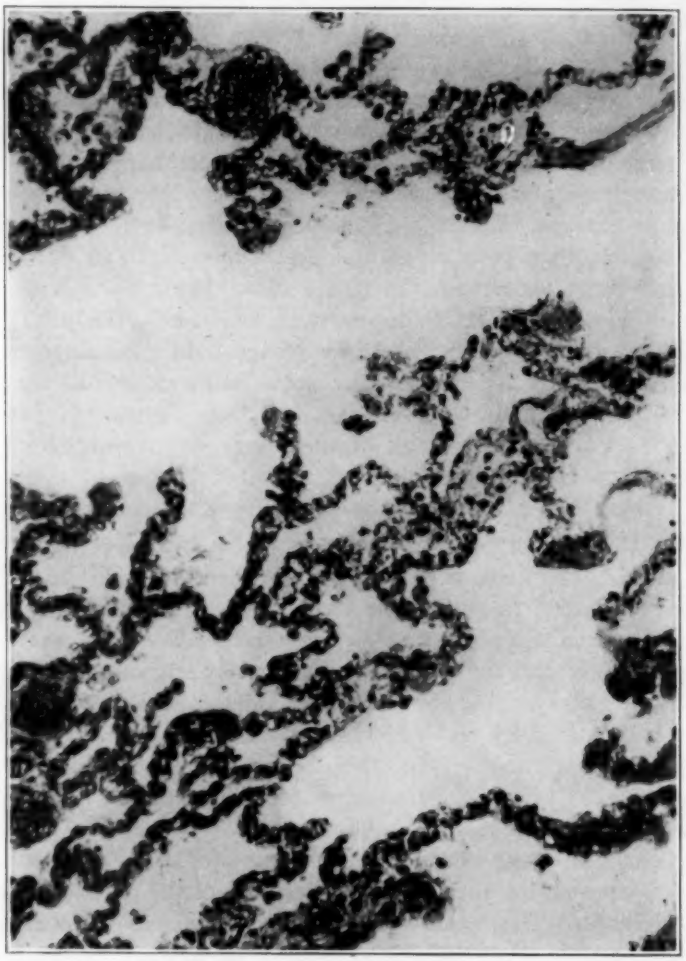

Fig. 4.—Lung (× 210) from a case of trauma to the abdomen with open hemorrhage into the peritoneal cavity and early death. Note congestion of the alveolar capillaries and "heart failure" cells lying in the alveolar spaces.

observed. Since fluids were administered by the intravenous route to nearly all these patients, the relatively minimal pulmonary edema observed needs some explanation.

Early Death with Closed Hemorrhage.—In this group of 5 cases the pathologic features resembled those seen in patients dying from open

hemorrhage with one exception, that the lungs showed edema, with red blood cells and "heart failure" cells in the alveolar spaces (fig. 5). The distribution of visceral weights in this group is shown in figure 6.

In fatal open hemorrhage the visceral changes are similar to those seen in closed hemorrhage except for the pulmonary edema which is

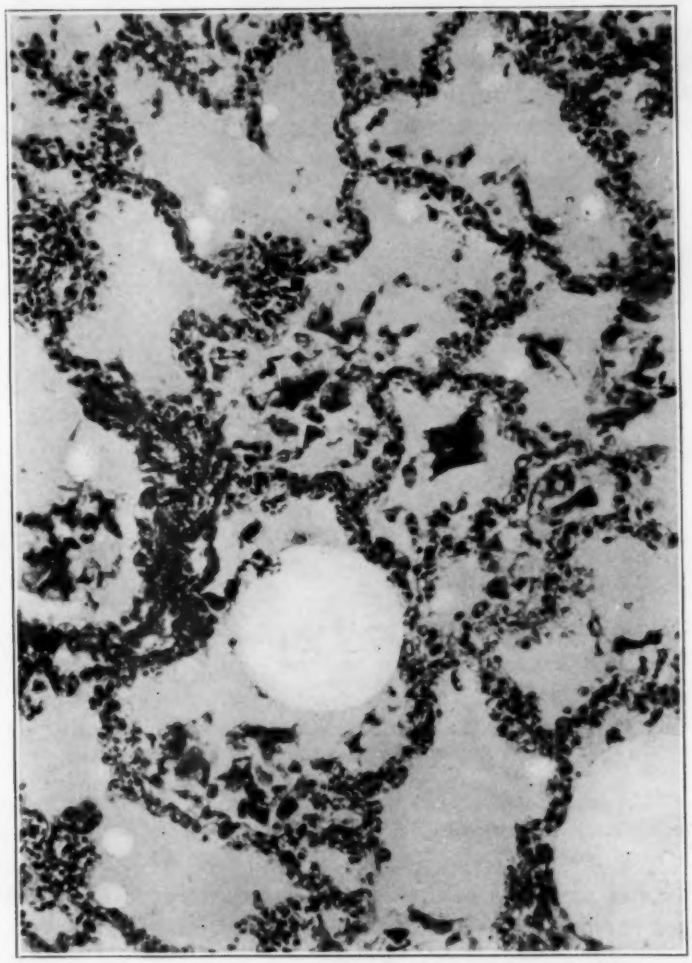

Fig. 5.—Lung (× 210) from a case of trauma to the abdomen with closed hemorrhage into the retroperitoneal tissues and early death. Note pulmonary edema, congestion of the alveolar capillaries and "heart failure" cells.

associated with the closed variety. Macrophage cells containing iron pigment are present in the alveoli in both types of hemorrhage but are more numerous in the closed type.

What explanation can be offered for this dissimilarity in the pulmonary observations, especially since both groups of patients have been given fluids intravenously? The difference may be explainable on the basis of an anoxemia of the central nervous system. The pathologic picture of anoxemia of the brain resulting from a rapid increase of intracranial pressure includes pulmonary congestion and edema. Such an anoxemia may result, however, from a reduction of the total blood volume. The rate of the reduction of the volume of blood must be considered in this connection. When the bleeding is rapid, as in an open type of hemorrhage, death takes place too rapidly to permit the

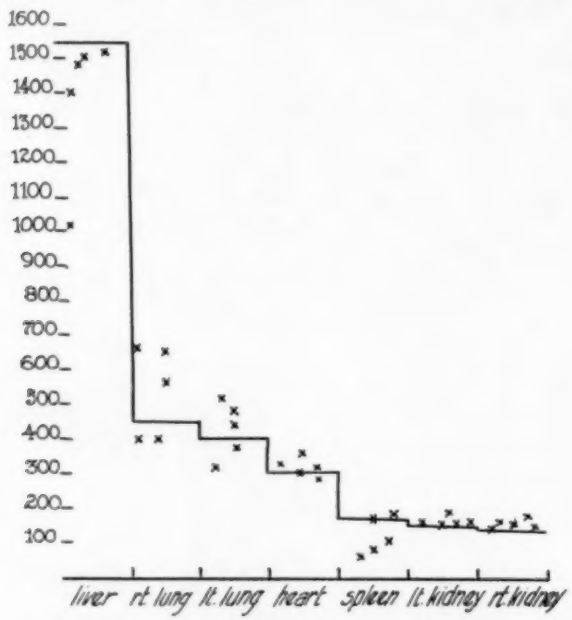

Fig. 6.—Distribution of visceral weights in 5 cases of trauma to the abdomen, thorax or extremities with closed hemorrhage and early death.

full effects of anoxemia of the nervous system to develop. When, on the other hand, the rate of bleeding is slower, as in the closed form of hemorrhage, anoxemia of the central nervous system is of longer duration and becomes more apparent in its effects on the viscera. This may explain the presence of pulmonary edema, which forms part of the pathologic picture associated with anoxemia of the brain in the closed form of hemorrhage. It may explain, also, the pulmonary edema and vascular congestion of the viscera which occur in those patients who die with either open or closed hemorrhage after forty-eight hours. In such patients the anoxemia of the central nervous system has been

prolonged enough to produce an effect on the vascular bed of the viscera. It becomes apparent from this discussion that any agent which reduces the effective and/or total blood volume may produce thereby an anoxemia of the central nervous system and its resultant pathologic picture of pulmonary edema and congestion with visceral vascular congestion. When the blood volume is much reduced, the presence of these visceral vascular changes may be hidden.

Early Death with Segregation of Blood.—In three of the 50 cases the estimated loss of blood from the circulation was insufficient to explain the fatal outcome. Examination, however, always revealed the presence of a segregation of blood in some part of the venous system as a result of the mechanical pressure of a collection of blood at some strategic point. Such a situation develops, for instance, when hemopericardium develops following a cardiac wound or when a retroperitoneal hemorrhage compresses the inferior vena cava. Hepler and Simonds [6] have also emphasized the importance of a segregation of blood in the production of shock. The pathologic change associated with a regional segregation of blood is a vascular congestion of the viscera below the point of venous obstruction. It should be pointed out again that in this group of cases the usual anatomic changes of hemorrhage are not found. Congestion of the spleen and edema of the lung (fig. 7) were constant additional findings. The diminution of cardiac output associated with the segregation of blood in the venous side of the circulation leads to anoxemia of the central nervous system, and this, in turn, accentuates the vascular distention of the viscera. The visceral weights were always increased (fig. 8). The clinical recognition of the occurrence of a regional segregation of blood is most important, inasmuch as the administration of fluids to such patients is definitely harmful, for it increases the rate of circulation and therefore forces the blood more rapidly into the segregated area.

Early Death with Infection.—Only 1 of the 50 patients in this series came under this heading. In this patient death resulted from a Clostridium welchii infection of the area of traumatized muscle of the abdominal wall after a gunshot wound. The essential features of the case were mild hemoconcentration, widespread vascular congestion of the viscera and hemolysis, as evidenced by the large amounts of iron pigment in the spleen, liver and lungs. Such an infection is liable to complicate a gunshot wound of the abdomen when the bullet has perforated the bowel wall and then lodged in the abdominal musculature.

6. Hepler, O. E., and Simonds, J. P.: Mechanism of Shock: Effects of Intravenous Injection of Salt Solution in Collapse Induced by Mechanical Impounding of Splanchnic Region in Normal and Hyperthyroid Dogs, Arch. Path. **25**:149-159 (Feb.) 1938.

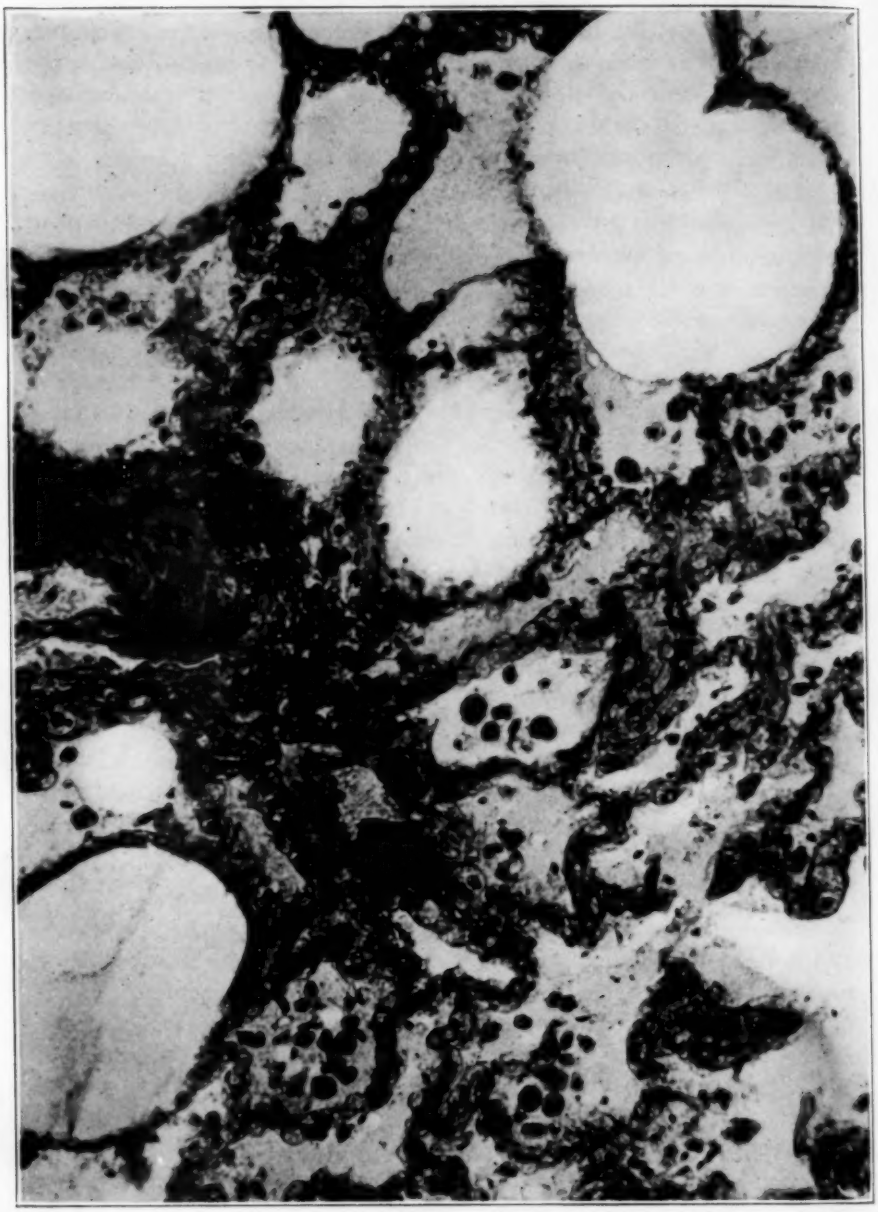

Fig. 7.—Lung (× 210) from a case of trauma to the thorax, with regional segregation of blood and early death. Note pulmonary edema, congestion of the alveolar capillaries, diapedesis of erythrocytes and "heart failure" cells.

It is well known that such an infection may be fulminating in character and that death may occur as early as seven hours after the injury. It is important, therefore, that this possibility be borne in mind and that appropriate cultures be taken after death from the site of trauma. Such cultures sometimes reveal the presence of this group of organisms.

The fulminating infection may be accompanied by symptoms which closely resemble those of shock. The general pathologic changes are

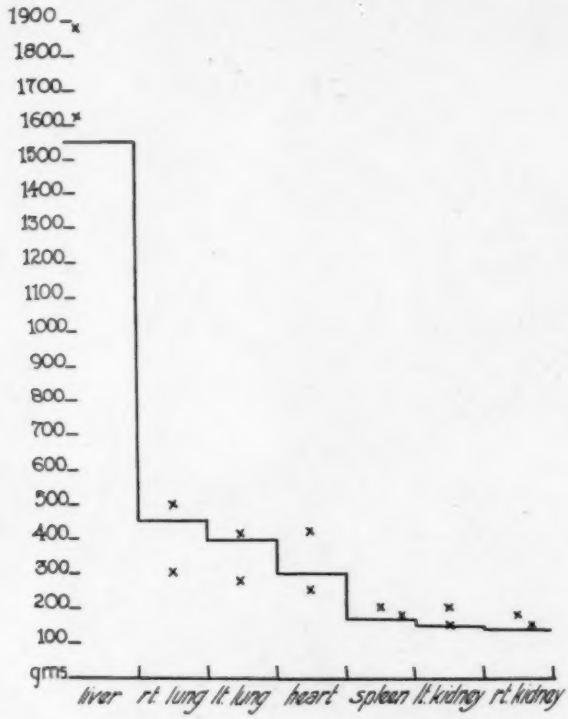

Fig. 8.—Distribution of visceral weights in 2 cases of trauma to the abdomen, thorax or extremities with regional segregation of blood and early death.

intense congestion of the vascular bed, with increased vascular permeability. There is marked hemolysis, and iron-containing pigment is deposited in the lungs, liver and spleen. The liver may show fatty metamorphosis, but may not if death occurs very rapidly. The lungs are edematous and extremely congested. The blood picture, as in the case reported, reveals hemoconcentration and leukocytosis. It seems likely that some cases of this type have not heretofore been recognized as resulting from such infections and perhaps have been used as presumptive evidence to support the toxic theory of traumatic shock.

Delayed Death with Open or Closed Hemorrhage.—There were 9 patients whose deaths occurred more than forty-eight hours from the time of injury. In every case evidences of infection were present, though the form varied. There were no anatomic evidences of open hemorrhage, and extreme splenic contraction was not usually present.

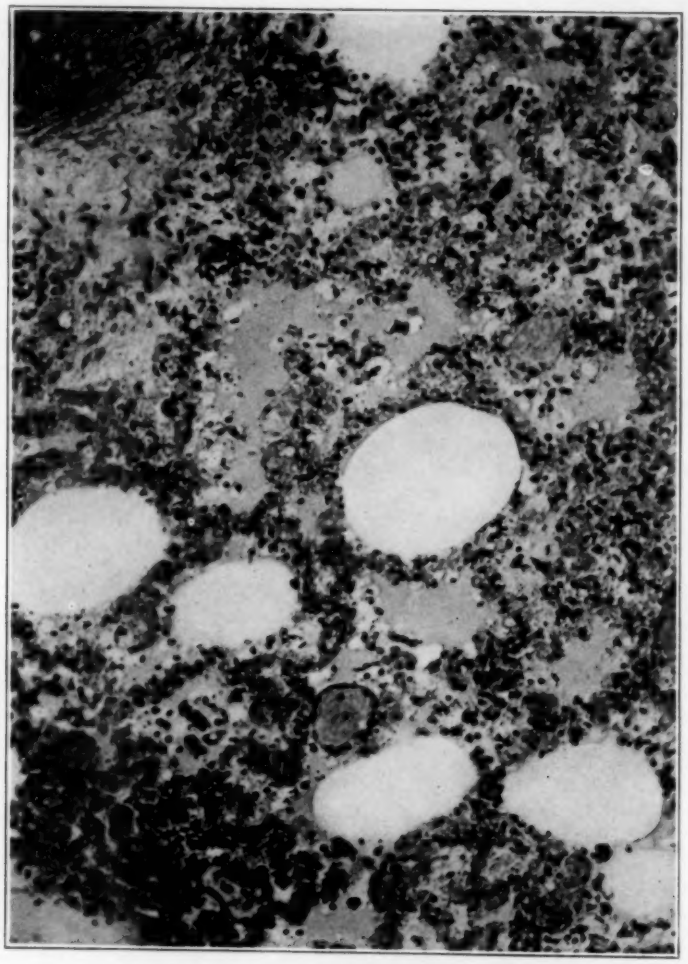

Fig. 9.—Lung (× 210) from a case of trauma to the abdomen with slow open hemorrhage and delayed death. Note pulmonary edema, congestion of the alveolar capillaries and "heart failure" cells.

In many cases the pathologic changes associated with early peritonitis were observed.

Pulmonary edema was, on the whole, more marked in the group whose deaths were delayed than in the group whose deaths occurred

earlier (fig. 9). In most patients a peculiar type of pneumonia was present, which varied greatly in extent. The edema present was patchy. The alveoli in certain areas were filled with only a pink-staining fluid with a variable admixture of large mononuclear cells containing an iron pigment. In other alveoli and bronchi the pink-staining fluid had been invaded by numerous polymorphonuclear leukocytes, and evidences of

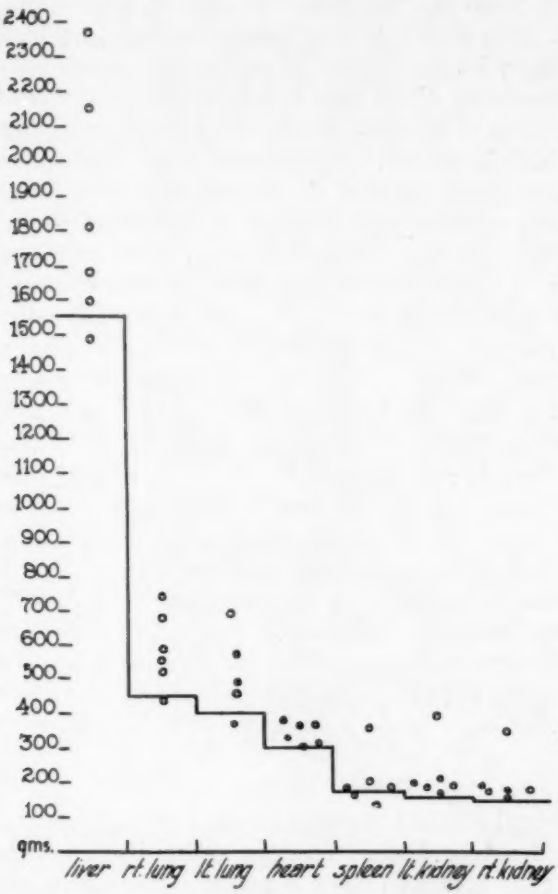

Fig. 10.—Distribution of visceral weights in 6 cases of trauma to the abdomen, thorax or extremities with open hemorrhage and delayed death.

fibrin formation were present. Many pigment-containing mononuclear cells lay side by side in the alveoli with polymorphonuclear leukocytes. Congestion of the alveolar capillaries was extreme.

Another histologic feature of interest was observed in these cases of delayed death, an apparently increased breakdown of the red blood cells. This was most marked in the spleen, in which much iron-containing pigment was found free in the tissues or lying within the large

mononuclear cells. Iron-containing pigment was also present in increased amounts within the mononuclear cells of the lungs and in the Kupffer cells of the liver. The increased hemolysis was noted in patients with open as well as in patients with closed hemorrhage. It was not dependent on the presence of infection, but when it was associated with it the degree of erythrocytic destruction was increased, particularly when the infection was due to Cl. welchii and related organisms. The distribution of visceral weights in this group is illustrated in figure 10.

The importance of the time factor in the production of the visceral changes is clearly illustrated in cases of thoracic and abdominal injuries in which death is delayed. The visceral anemia and splenic contraction present in the early stages of shock give place, when death is deferred, to vascular congestion and increase in weight of the viscera. Pulmonary edema also becomes more evident, as do the signs of increased destruction of red blood cells, and large amounts of iron pigment may be seen in the lungs, the liver and, in particular, the spleen.

Several factors must be taken into consideration when these changes are discussed. Three of these considerations seem to be especially important: 1. With the longer duration of life there is likely to be a larger administration of intravenous fluids. 2. Infection, variable in degree, is likely to supervene. 3. Prolonged low blood pressure is likely to lead to anoxemia of the central nervous system, with resulting visceral vasodilatation and an alteration in the permeability of the capillaries, particularly the pulmonary capillaries.

It is essential to recognize the important role played by anoxemia of the central nervous system in the production of visceral vasodilatation and pulmonary changes. This factor, it should be emphasized, is present in every form of shock, though its effects may be masked if an extreme reduction of blood volume occurs before death.

TRAUMA DUE TO BURNS

The visceral changes present in early and late deaths from thermal trauma need not be discussed in any great detail. Patients who die soon after their injuries usually reveal a diminution of the weights of the various viscera (fig. 11), contraction of the spleen and other evidences of a rapid reduction of the total blood volume. Fatty metamorphosis of the liver, widespread petechial hemorrhages and other signs suggestive of the presence of a circulating toxin are sometimes observed in patients who die as early as five hours after the receipt of the burn.

When death is delayed after burns, evidences are found of widespread vascular congestion, an increase in the visceral weights (fig. 11), an absence of splenic contraction, widespread petechial hemorrhages and marked pulmonary edema. There is also present an excessive destruc-

tion of red blood cells, associated with the presence of large amounts of iron-containing pigment in the spleen, liver and lungs. Whether the hemolysis is due to the action of a circulating toxin or to excessive activity of the reticuloendothelial system cannot be stated definitely at this time. We have not found necrosis of the liver, which has been noted by various observers, e. g., Belt,[7] although fatty metamorphosis of the liver is a frequent finding.

Considerable discussion has arisen as to the cause of the hypotension associated with trauma due to burns. One group of observers has

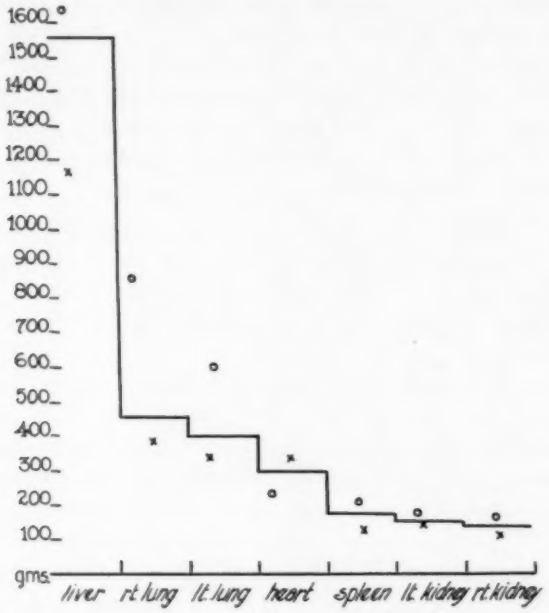

Fig. 11.—Distribution of visceral weights in 2 cases of burns. x = early death; o = delayed death.

ascribed a major role to the toxins released from the burned area (Bardeen[8]). A second group has held that the fall is due to a shift of fluid into the burned area (Underhill and co-workers,[9] Harkins[10]). Still

7. Belt, T. H.: Liver Necrosis Following Burns, Simulating the Lesions of Yellow Fever, J. Path. & Bact. **48**:493-498 (May) 1939.

8. Bardeen, C. R.: A Review of the Pathology of Superficial Burns with a Contribution to Our Knowledge of the Pathological Changes in the Organs in Cases of Rapidly Fatal Burns, Johns Hopkins Hosp. Rep. **7**:137-179, 1898.

9. Underhill, F. P.; Carrington, G. L.; Kapsinow, R., and Pack, G. T.: Blood Concentrations in Extensive Superficial Burns, and Their Significance for Systemic Treatment, Arch. Int. Med. **32**:31-49 (July) 1923.

10. Harkins, H. N.: Experimental Burns: I. Rate of Fluid Shift and Its Relation to the Onset of Shock in Severe Burns, Arch. Surg. **31**:71-85 (July) 1935.

another group has maintained that the early fall in blood pressure is due to loss of fluid into the traumatized area and that later hypotension is due to a toxemia (Wilson and co-workers [11]). The argument is still unsettled.

TRAUMA DUE TO OPERATION

Numerous factors are involved in the syndrome of shock following surgical procedures. I have excluded from this series such complications as postoperative infections, pulmonary embolism and similar conditions. This process of exclusion leaves 4 cases, which are grouped under the heading of shock due to operative trauma.

In the fatalities following surgical procedures within the abdomen in this series, shock was always associated with marked vascular congestion of the splanchnic area. The organs were increased in weight, and the spleen was congested (fig. 12). As has been pointed out, vasoconstriction of the splanchnic area normally follows a reduction of blood volume (Davis and Jermstad [12]), but in these cases, in spite of large losses of blood, this did not occur. Instead, a vasodilation was present, which, in fact, might have resulted from the direct trauma of the intra-abdominal operation. The significance of anesthesia, particularly of spinal anesthesia, must also be considered in the production of these vascular changes.

The extent of the vasodilatation is difficult to determine. In operations within the peritoneal cavity, it is chiefly confined to the splanchnic area. The lungs are only moderately congested, and pulmonary edema is not a conspicuous or a constant feature. In the particular group of cases under discussion the phenomena of vasodilatation were always accompanied by open or by closed hemorrhage, but the amount of blood lost was not in itself sufficient to cause death if a normally reacting splanchnic vascular bed had been present. A compensatory splanchnic vasoconstriction, however, had not occurred in these cases. It is therefore apparent that in postoperative shock one is confronted by two phenomena: vasodilatation of varying degrees and a reduction of the blood volume. The combination of these phenomena accentuates the state of shock.

At this point it is possible to sum up as follows the factors which influence visceral changes in patients dying from shock due to various forms of trauma:

1. The site of the trauma, e. g., whether to the central nervous system, the abdomen, the thorax or other organs.

2. The mode of production of the trauma, e. g., by a bullet wound or a surgical operation.

11. Wilson, W. C.; Jeffrey, J. S.; Roxburgh, A. N., and Stewart, C. P.: Toxin Formation in Burned Tissues, Brit. J. Surg. **24**:601-611 (Jan.) 1937.

12. Davis, H. A., and Jermstad, R. J.: Regional Distribution of Blood in Experimental Secondary Shock, Arch. Surg. **38**:556-580 (March) 1939.

3. The rate of reduction of the effective and/or total blood volume.

4. The duration of shock.

5. The total blood volume at the time of death.

6. The presence or absence of a regional segregation of blood.

7. The mechanism of production of shock: by vasodilatation, as in cerebral injuries and surgical operations, or by reduction of the blood volume, as in open or closed hemorrhage.

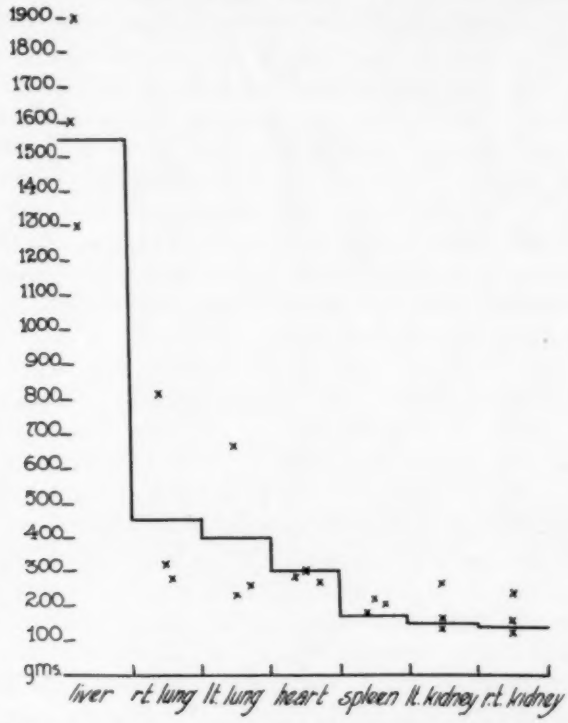

Fig. 12.—Distribution of visceral weights in 3 cases of trauma following surgical procedures.

8. The presence of a circulating toxin, as in burns or in fulminating gas bacillus infections.

9. The intravenous administration of fluids.

Finally, it might be pertinent to discuss the significance of certain less common pathologic changes. Some emphasis has been placed on the frequent presence of subendocardial hemorrhage in patients dying from obstetric shock (Sheehan [13]). Such hemorrhages have also been found in patients dying from burns (Bardeen [8]), from gunshot wounds

13. Sheehan, H. L.: The Pathology of Obstetric Shock, J. Obst. & Gynaec. Brit. Emp. **46**:218-231 (April) 1939.

(Moon and Kennedy;[1] Külbs and Strauss[14]) and from cerebral injuries of various types (Sheehan[13]). In this series the presence of subendocardial hemorrhages has been noted in 3 patients, the first of whom died of cerebral injury, the second from asphyxia following a gunshot wound of the neck with bleeding into the anterior mediastinum and compression of the trachea, and the third from a gas bacillus infection following a gunshot wound of the abdomen.

Petechial hemorrhages were found most frequently in the pulmonary alveoli. They occurred almost constantly in death from cerebral trauma but were also seen in the lungs of patients suffering from burns or from closed or open hemorrhage and dying a late death. A peculiar form of petechial hemorrhage was noted in the spleens of patients dying from cerebral injury or from a slow open or closed hemorrhage into some other region of the body. Such petechial hemorrhages presented themselves in the malpighian lymphatic nodules of the spleen and appeared to surround the central arteriole. In many instances the entire lymphoid tissue of the nodule was replaced by a pool of blood. Petechial hemorrhages were seen, in addition, in the renal pelves, the ureters, the gastrointestinal mucosae and the adrenal glands in another 5 patients in this series. The cause of death was cerebral trauma in 1 case, burns in 2 cases, a gunshot wound of the abdomen with hemoperitoneum in 1 case and a gunshot wound of the liver and biliary peritonitis in 1 case.

It is evident that the occurrence of these petechial hemorrhages, especially in cases of simple compression of the brain by an extradural blood clot, cannot be explained adequately by those hypotheses which support the presence of a circulating toxin in secondary shock. Hemodynamic alterations in the form of rapid and violent changes in blood pressure would appear to offer a more inclusive explanation. In conclusion, it might be stated that it was possible to observe the frequent occurrence of macrophage cells containing an iron-pigment ("heart failure" cells) in the pulmonary alveoli of patients dying from shock associated with cerebral and other forms of trauma. This is not in agreement with the findings of Moon and Kennedy,[1] who have stated that such cells are not found in the lungs of patients dying from shock.

SUMMARY AND CONCLUSIONS

A study has been presented of visceral changes occurring in shock resulting from injuries to the head, the thorax, the abdomen and the extremities, from burns and from surgical operations. The study is based on an analysis of 50 cases, in all of which postmortem examination was performed within one to three hours after death.

The visceral changes are influenced by a variety of factors, which are enumerated and discussed.

14. Külbs, F., and Strauss, H.: Ueber subendokardiale Blutungen, Klin. Wchnschr. **12**:933 (June) 1933.

The study of the syndrome of shock will be aided by investigations of the pathologic changes which occur in the tissues.

A tentative pathologic grouping of the cases is set forth, not based on or biased by any specific theory of shock, but dependent solely on the pathologic changes observed at the autopsy table or under the microscope.

It is suggested that such a grouping of cases is likely to aid in a more searching analysis of the syndrome of shock.

The significance of anoxemia of the central nervous system in all forms of shock is emphasized in relation to the production of the pathologic changes.

ILLUSTRATIVE CASE REPORTS

CEREBRAL TRAUMA

CASE 1.—E. S., a white man aged 31, was admitted to the John Gaston Hospital in Memphis in an unconscious state. He was thought to have been "slugged over the head." The temperature was 103 F., the pulse rate 60 per minute, the respiratory rate 40, and the blood pressure 110 systolic and 70 diastolic. The essential physical findings were a bruised area over the right eye, unequal dilatation of the pupils and rigidity of the left leg. Death occurred twenty minutes after admission, before any treatment could be instituted.

Autopsy.—No fluid was present in the pleural or peritoneal cavities. The heart weighed 350 Gm. The right lung weighed 700 Gm. and the left 400 Gm. Both were firm and dark purplish. Thin, bright red fluid exuded from the cut surfaces; the bronchi were filled with a pink, frothy fluid. The spleen weighed 370 Gm. It was slate blue and very soft. The splenic pulp was soft and hemorrhagic and scraped readily. The liver weighed 2,240 Gm. It was smooth and reddish brown. The gastrointestinal tract revealed moderate congestion of the gastric mucosa. The right kidney weighed 190 Gm. and the left 200 Gm. Both revealed vascular congestion of the cortex and medulla.

Examination of the head revealed a subcutaneous hematoma over the right parietal and frontal regions and a Y-shaped fracture of the skull, without depression. A large extradural clot (11.5 by 8.5 by 4 cm.) compressed the right frontal and parietal lobes of the brain. There was no gross destruction of the brain tissue.

Microscopic examination of the lungs revealed congestion of the alveolar capillaries and considerable fluid in the alveoli and bronchioles. Red blood cells were found in the alveoli and bronchioles, and there was a moderate number of "heart failure" cells. The spleen was markedly congested. Red blood cells appeared to be undergoing hemolysis. There was much iron-containing pigment inside the macrophages and also lying free. There was moderate congestion of the blood vessels of the liver, and swelling and vacuolation of the liver cells. No iron-containing pigment was present.

CASE 2.—J. W., a Negro man aged 29, was admitted to the John Gaston Hospital in Memphis in an unconscious state, with a gunshot wound of the head. The pulse rate was 120 per minute and the blood pressure 106 systolic and 60 diastolic. Death occurred within six hours.

Autopsy.—No fluid was found in the pleural or peritoneal cavities. The heart weighed 340 Gm. The chambers were not dilated. The right lung weighed 720 Gm. and was soft, elastic and air containing. The left lung weighed 640 Gm. and

was congested at the base. The spleen weighed 160 Gm. It was firm and dark red. The liver weighed 1,580 Gm. and presented no gross pathologic changes. There were no gross changes in the gastrointestinal tract. The right kidney weighed 180 Gm. and the left 170 Gm.

Examination of the head revealed hemorrhage into the tissues of the scalp. The dura mater was torn at the sites of entrance and exit of the bullet, and at these points large hematomas lay beneath the dura. There was marked destruction of the tissue of the left cerebral hemisphere.

Microscopic examination of the lungs revealed considerable emphysema. There was marked congestion of the alveolar capillaries, and fluid and red blood cells were found in the alveolar spaces. There was a moderate number of "heart failure" cells. The sinusoids and capillary spaces of the spleen were markedly congested, and many macrophage cells contained iron pigment. The capillaries of the liver were congested in the region of the central veins. The kidneys revealed marked vascular congestion and parenchymatous degeneration of the tubular epithelium. Examination of the brain revealed hemorrhage into the cerebral tissue, with necrosis and infiltration by polymorphonuclear leukocytes. Phagocytic mononuclear cells contained iron pigment. The remaining viscera showed congestion of the capillaries.

TRAUMA TO ABDOMEN AND THORAX

Early Death with Open Hemorrhage.

CASE 3.—J. C., a Negro man aged 59, was admitted to the John Gaston Hospital in Memphis with a gunshot wound of the upper part of the abdomen. The intravenous administration of fluids was without avail, and death occurred eight hours later.

Autopsy.—The peritoneal cavity contained 1,800 cc. of fluid and clotted blood. There was no fluid in the pleural cavities. The heart weighed 470 Gm., and the left ventricle was hypertrophied. The right lung weighed 400 Gm. and the left 360 Gm. Both presented mild congestion. The spleen weighed 80 Gm. and was dry and contracted. The liver weighed 1,680 Gm., and there was a large laceration, surrounded by hemorrhage, in the left lobe. Examination of the gastrointestinal tract gave essentially negative results. There was no evidence of vascular congestion, and the vessels were contracted and contained little blood. The right kidney weighed 160 Gm. and was pale. The left weighed 210 Gm., and the upper pole was lacerated by the passage of the bullet.

Microscopic examination of the lungs revealed marked emphysema but no edema. There were many "heart failure" cells in the alveolar wall and alveolar spaces. Examination of the liver revealed hemorrhage into the tissue, with mild early inflammatory cell invasion. The adjacent liver cells were edematous. Examination of the kidney revealed considerable hemorrhage into the renal tissue, with an infiltration by polymorphonuclear leukocytes.

Comment.—The case just described illustrates that trauma to an organ, especially by a bullet, causes an increase in its weight, which is partly due to an infiltration of blood into the tissues and partly to an imbibition of fluid from the capillaries by the injured or dying cells. In some instances the fluid shift into an injured viscus may represent a considerable loss from the general circulation. The increase in weight of an injured viscus must therefore be taken into consideration in estimating the total diminution of the effective blood volume.

Early Death with Closed Hemorrhage.

CASE 4.—L. P., a Negro youth aged 17, was struck by an automobile two hours before admission to the John Gaston Hospital in Memphis. Examination revealed a compound fracture of the left tibia and fibula, a laceration of the left inguinal region, dislocation of the right hip joint, and comminuted fractures of the pelvis on the right side. The temperature was 100.6 F., the pulse rate 145 per minute, the respiratory rate 68 and the blood pressure 130 systolic and 80 diastolic. The red cell count was 4,000,000. The intravenous administration of fluids was without avail, and death occurred within eight hours.

Autopsy.—The injuries already listed were found on postmortem examination, and, in addition, a badly comminuted fracture of the pelvic arch on the left side. There was a small amount of blood (50 cc.) in the pelvis, and several large hematomas were present in the mesentery of the small intestine. In the lower portion of the pelvis was a massive retroperitoneal hemorrhage which extended into the fat around the urinary bladder. There was no fluid in the pleural cavities. The heart weighed 320 Gm. and was contracted but revealed no other pathologic change. The right lung weighed 400 Gm. and the left 320 Gm.; both revealed moderate congestion and edema. The spleen weighed 80 Gm. and was contracted and pale. The liver weighed 1,020, Gm. and was pale and bloodless. The gastrointestinal tract was pale and the blood vessels contracted. The left kidney weighed 160 Gm. and the right 150 Gm.; both were pale.

On microscopic examination the lungs showed marked congestion of the alveolar capillaries. Fluid was present in the alveoli, together with red blood cells and "heart failure" cells. Examination of the spleen revealed the sinusoids and blood vessels to be empty of blood. The liver cells were moderately swollen and granular; there was no congestion of the blood vessels. The brain revealed congestion of the meningeal vessels.

CASE 5.—L. M., a Negro man aged 24, suffered a stab wound of the abdomen thirty minutes before admission to the John Gaston Hospital in Memphis. The temperature was 96 F., the pulse rate 120 per minute and the blood pressure 76 systolic and 50 diastolic. The red blood cell count was 3,200,000, the white blood cell count 8,200, and the hemoglobin 9.4 Gm. per cent. The intravenous administration of fluids was without avail, and death occurred at the end of ten and a half hours.

Autopsy.—Large hematomas were found in the left psoas muscle. There was no fluid or blood in the peritoneal cavity or the pleural cavities, but large hematomas were found in the mesentery of the small intestine and the transverse mesocolon. The heart weighed 300 Gm. It was contracted, and the myocardium was pale. The right lung weighed 650 Gm. and the left 480 Gm. The lung tissue on both sides was dark reddish purple and firmer than normal. A thin reddish fluid could be squeezed from the cut surfaces. The spleen weighed 90 Gm. and was contracted and relatively bloodless. The liver weighed 1,480 Gm., and the parenchyma was pale. The gastrointestinal tract was pale and presented no evidence of vascular congestion. The left kidney weighed 150 Gm. and the right 140 Gm. The parenchyma was pale.

Microscopic examination of the lungs showed marked congestion of alveolar capillaries. Many alveolar spaces were filled with fluid, red blood cells and numerous macrophage cells containing iron pigment. Occasional areas of emphysema and atelectasis were observed. Examination of the spleen revealed that the sinusoids and capillaries contained little or no blood; there were no evidences of free blood pigment. There was cloudy swelling of the hepatic cells; the central vessels were not congested. There was cloudy swelling of the epithelium of the convoluted tubules of the kidneys.

Early Death with Regional Segregation of Blood.

CASE 6.—T. M., a white man aged 23, suffered a stab wound of the left side of the chest at the fifth intercostal space in the midclavicular line. The injury occurred half an hour before he was admitted to the John Gaston Hospital in Memphis, and death took place before treatment could be instituted.

Autopsy.—There was no fluid in the pleural or peritoneal cavities. The pericardial cavity contained 500 cc. of freshly clotted blood. There was an incised wound of the right ventricle on the anterior surface. The left lung weighed 500 Gm. and the right 650 Gm. Both were dark red and firm, and frothy fluid could be expressed from the cut surfaces. The spleen weighed 200 Gm. It was dark blue, firm and congested. The liver weighed 1,800 Gm. and exhibited moderate vascular congestion. The gastrointestinal tract revealed congestion of the mesenteric vessels. The right kidney weighed 160 Gm. and the left 180 Gm. The cortex and medulla were congested.

Microscopic examination of the lungs revealed marked congestion of the alveolar capillaries. The alveolar spaces were full of fluid, and there were many "heart failure" cells. Examination of the spleen revealed the blood vessels congested and much iron pigment present. The remaining viscera showed vascular congestion.

Early Death with Infection.

CASE 7.—A. M., a Negro man aged 53, suffered a gunshot wound of the left upper quadrant of the abdomen half an hour before admission to the John Gaston Hospital in Memphis. The temperature was 95 F., the pulse rate 120 per minute, the respiratory rate 24, and the blood pressure 60 systolic and 40 diastolic. The red blood cell count was 5,220,000 and the white blood cell count 27,450. The intravenous administration of fluids was without avail, and death occurred within twenty-eight hours.

Autopsy.—The peritoneal cavity contained 500 cc. of grape juice–colored fluid, and the left pleural cavity, 150 cc. of straw-colored fluid. There was no fluid in the right pleural cavity. The pericardial cavity contained 15 cc. of clear fluid. All the tissues of the posterior abdominal wall were discolored by extensive interstitial hemorrhage and were markedly swollen and soft in consistency. Anaerobic cultures from this area were made within an hour after death and revealed a growth of Cl. welchii and Bacillus coli. The tissues of the left renal fossa were hemorrhagic.

The heart weighed 340 Gm. and was contracted. The right lung weighed 660 Gm. and the left 510 Gm. Both were dark reddish purple and firmer than normal. Reddish, frothy fluid could be expressed from the cut surfaces. The spleen weighed 180 Gm. and was firm in consistency. The surface was dark blue and the cut surfaces reddish brown. The stomach and small intestine were dilated with gas, but the remainder of the gastrointestinal tract revealed nothing of note. The pancreas showed a moderate amount of hemorrhage into the tissues surrounding the distal half. The right kidney weighed 170 Gm. and the left 180 Gm. Both showed a moderate degree of vascular congestion.

Microscopic examination of the lungs showed fluid in the alveoli. Numerous "heart failure" cells containing iron pigment were observed, and the red blood cells in the alveoli were undergoing hemolysis. The spleen revealed extreme engorgement of the blood vessels with red blood cells, many of which were undergoing disintegration; much iron containing pigment was noted. The central capillaries of the liver were moderately engorged with blood. There was parenchymatous degeneration of the liver cells, and the Kupffer cells contained iron pigment. The intertubular capillaries of the kidneys, as well as the glomerular

capillaries, were congested. The remaining viscera showed a moderate grade of vascular congestion.

Delayed Death with Open Hemorrhage.

CASE 8.—D. W., a Negro man aged 22, was admitted to the John Gaston Hospital in Memphis shortly after he had sustained a bullet wound of the left side of the chest. Dyspnea was present, and rapidly increased. Nine hundred cubic centimeters of blood was removed from the left thoracic cavity two days after admission. The bleeding continued, and death occurred four days later.

Autopsy.—The mucous membrane and skin were pallid. No fluid or blood was present in the peritoneal cavity. The left pleural cavity contained 1,500 cc. of blood, which was partially coagulated. There was no fluid in the right cavity. The left lung was airless and collapsed; the right lung was voluminous, moist and congested. The heart weighed 300 Gm; it revealed no significant changes. The spleen weighed 340 Gm. and was soft; the pulp scraped readily. The liver weighed 1,600 Gm. and was pale. The left kidney weighed 220 Gm. and the right 200 Gm. The remaining viscera showed no changes.

Microscopic examination of the lungs revealed congestion of the alveolar capillaries. The alveolar spaces were filled with fluid, fibrin, polymorphonuclear leukocytes and large mononuclear cells which contained brown pigment. The spleen showed cellular hyperplasia. The kidneys revealed cloudy swelling of the tubular epithelium of the convoluted tubules.

TRAUMA DUE TO BURNS

Early Death.

CASE 9.—B. Y., a Negro woman aged 26, was admitted to the John Gaston Hospital in Memphis with extensive burns of the body. The red blood cell count was 6,176,000 and the white blood cell count 38,000; the hemoglobin was 19 Gm. per hundred cubic centimeters. Intravenous fluids were administered, but no improvement was observed, and death occurred five hours after admission to the hospital.

Autopsy.—Extensive burns covered the body from head to foot. The upper portion of the body presented second degree burns, and the lower portion, third and fourth degree burns. No free fluid was observed in the peritoneal or pleural cavities. The pericardial sac contained 10 cc. of clear straw-colored fluid. The heart weighed 340 Gm. and was contracted. The right lung weighed 385 Gm. and the left 350 Gm. Both were congested and edematous, and frothy fluid exuded from the cut surfaces. The spleen weighed 120 Gm. and was moderately firm. The cut surface was dark and reddish purple. The liver weighed 1,160 Gm. and was of normal consistency. The color was pale yellowish brown. The gastrointestinal tract presented no changes. The right kidney weighed 110 Gm. and the left 140 Gm. Both were dark purple. On the right side were numerous petechial hemorrhages into the mucosa of the pelvis and the upper end of the ureter. The remaining viscera presented no gross pathologic changes.

Microscopic examination revealed that the alveolar capillaries of the lungs were extremely congested. The alveoli contained considerable fluid, in which were red blood cells and desquamated alveolar epithelium. Occasional "heart failure" cells containing iron pigment were observed. The sinusoids and capillaries of the spleen were markedly congested, and increased amounts of iron pigment were present. The liver revealed mild fatty metamorphosis. The tubular epithelium of the kidneys had undergone marked parenchymatous degeneration, and many of the tubules and glomeruli contained brownish pigment. The capillaries of the adrenal glands were congested, and the medullary tissue was edematous.

Delayed Death.

CASE 10.—F. L., a Negro woman aged 19, suffered first and second degree burns of the left arm, the right axilla, the back and the abdomen just before she was admitted to Charity Hospital of Louisiana at New Orleans. Fluids were administered intravenously to the limit of safety, but were without effect, and death occurred five days after the injury.

Autopsy.—The subcutaneous tissues of the entire body were found to be markedly edematous. There was no fluid in the peritoneal cavity. Each of the pleural cavities contained approximately 300 cc. of clear straw-colored fluid, and the pericardial cavity contained approximately 100 cc. of the same type of fluid. The heart weighed 250 Gm. and revealed no gross pathologic changes. The right lung weighed 750 Gm. and the left 600 Gm. Both were firm and reddish purple. Considerable frothy fluid escaped from the cut surfaces. The spleen weighed 220 Gm. It was firm and purplish brown. The liver weighed 1,600 Gm. It was yellowish brown and firm. The mucosa of the stomach and jejunum appeared diffusely hemorrhagic, with marked vascular congestion and numerous petechial hemorrhages. No evidences of ulceration were observed at any point along the gastrointestinal tract. The left kidney weighed 180 Gm. and the right 170 Gm. Both were firm and reddish brown. The right adrenal gland revealed no gross pathologic change; on the left side gross hemorrhage had occurred into the medulla and cortex of the gland.

Microscopic examination of the lung revealed marked congestion of the alveolar capillaries. Fluid, red blood cells and "heart failure" cells were observed in the alveolar spaces. In the spleen the sinusoids were packed with red blood cells undergoing disintegration. Large amounts of iron-containing pigments were present both within the macrophage cells and free in the tissues. Fatty metamorphosis was observed in the liver. The stomach wall revealed extreme congestion of the mucosal and submucosal capillaries, with free hemorrhage into the tissues. There was no necrosis of the epithelium. The glomerular capillaries of the kidney were markedly congested, and the tubular epithelium exhibited parenchymatous degeneration.

TRAUMA DUE TO OPERATION

CASE 11.—S. M. B., a Negro woman aged 36, was operated on at Charity Hospital of Louisiana at New Orleans for uterine fibroids. Subtotal hysterectomy was done, with the patient under ether anesthesia. Four hours after the operation she went into a state of shock from which she never emerged. There was no response to intravenous fluid therapy or to blood transfusion. Death occurred thirty-six hours after operation.

Autopsy.—The peritoneal cavity contained 1,000 cc. of blood. There was no fluid in the pleural cavities. The pericardial cavity contained 40 cc. of straw-colored fluid. The heart weighed 300 Gm. and was contracted. The right lung weighed 320 Gm. and the left 230 Gm. Both contained air and were pinkish gray. The spleen weighed 220 Gm. It was firm, dark blue and congested. The liver weighed 1,900 Gm. It was firm and reddish brown. The only pathologic change observed in the gastrointestinal tract was a moderate congestion of the mesenteric and omental blood vessels. The right kidney weighed 240 Gm. and the left 260 Gm. The blood vessels of the renal cortex and medulla were congested.

Microscopic examination revealed the alveolar capillaries of the lung to be markedly congested. Numerous "heart failure" cells were present in the alveolar spaces. No edema was observed. The sinusoids and capillaries of the spleen were markedly engorged with red blood cells. The capillaries in the neighborhood of the central veins of the liver were congested. The other viscera showed evidences of vascular congestion.

DIFFERENTIAL DIAGNOSIS OF MECHANICAL AND PARALYTIC ILEUS

WITH SPECIAL REFERENCE TO EARLY DIAGNOSIS OF STRANGULATED OBSTRUCTION

J. B. HAWORTH, M.D.
AND
L. H. GARLAND, M.D.
SAN FRANCISCO

A series of abdominal roentgenograms recently encountered at the San Francisco Hospital led us to review the subject of the differential diagnosis of intestinal obstruction from the roentgenologic standpoint and to make a tabular study.

From approximately 250 cases in which either a clinical or a roentgen diagnosis of intestinal obstruction was made, 100 cases were selected in which satisfactory roentgenograms were available and in which the diagnoses were established by observation made at operation or at postmortem examination or by what we considered incontrovertible clinical evidence. The distribution of these 100 cases according to final diagnosis is given in table 1.

The criteria by which the roentgenologic diagnosis of acute intestinal obstruction may be made have been outlined by Laurell,[1] Wangensteen,[2] Granger,[3] Eliason and Johnson[4] and many others. The differential diagnosis between distention from mechanical obstruction and distention from peritonitis (paralytic ileus) or from another cause has also been discussed.[5] We endeavored to select the more important of these criteria and tabulated our cases according to the relative frequency

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From the Department of Medicine (Division of Radiology) of the Stanford University School of Medicine and the Department of Public Health of the City of San Francisco (J. C. Geiger, Director).

1. Laurell, H.: Roentgenologic Signs of Abdominal Effusions: Roentgen Diagnosis of Peritonitis, Acta radiol. **5**:63-104, 1926.

2. (*a*) Wangensteen, O. H., and Paine, J. R.: Treatment of Acute Intestinal Obstruction by Suction with the Duodenal Tube, J. A. M. A. **101**:1532 (Nov. 11) 1933. (*b*) Wangensteen, O. H.: Rationalizing Treatment in Acute Intestinal Obstructions, Surg., Gynec. & Obst. **64**:273 (Feb. 15) 1937.

3. Ochsner, A., and Granger, A.: Roentgen Diagnosis of Ileus, Ann. Surg. **92**: 947-958 (Dec., pt. 1) 1930.

4. Eliason, E. L., and Johnson, J.: Diagnostic Features of Ileus, Radiology **26**:342-348 (March) 1936.

5. (*a*) Laurell.[1] (*b*) Ochsner and Granger.[3]

and severity of these findings in each of several common pathologic conditions. Each roentgenogram was scrutinized carefully, and the data given under the headings of table 2 were recorded.

By the separation of the cases into the clinicopathologic groups listed in table 2, a relatively high correlation of the data for each group was obtained. The presence of this high correlation leads us to believe that there exists a more or less characteristic pattern of findings in cases of

TABLE 1.—*Final Diagnoses in One Hundred Cases of Intestinal Obstruction or Paralytic Ileus*

Final Diagnosis	Roentgen Diagnosis (Proved)	
	I. Obstruction Group	
	Small Bowel Obstruction	Large Bowel Obstruction
Adhesions	27	1
Volvulus	2	4
Hernia	12	..
Carcinoma of colon	..	8
Fecal impaction	..	5
Mesenteric thrombosis	1	1
Regional ileitis	1	..
Intussusception	1	..
Gallstone impaction	1	..
Carcinoma of cervix with extension	1	..
	II. Ileus Group	
	Ileus with Peritonitis	Ileus without Peritonitis
Pelvic inflammatory disease	6	1
Perforated viscus	5	..
Appendicitis	7	..
Postoperative peritonitis	2	..
Cholecystitis	..	3
Acute enteritis	..	2
Diverticulitis	2	..
Peritonitis	2	..
Typhoid fever	..	1
Morphine addiction	..	1
Pyelitis	..	1
Functional vomiting	..	1

intestinal obstruction or paralytic ileus, which, considered with the clinical history, should enable the radiologist to arrive at an accurate diagnosis in most instances. The roentgenologic findings alone, however, are inadequate for diagnosis in about 15 per cent of cases; this is shown by the selected cases presented in table 3, which are illustrative of the possibilities of error when the clinical findings are not given due consideration.

An abnormal amount of gas was found distributed in various portions of the intestinal tract in all of our cases except the 2 instances of

TABLE 2.—*Differential Diagnostic Findings (Graded + to ++++ According to Severity) in Eighty-Seven Typical Cases of Intestinal Obstruction and Paralytic Ileus* *

Diagnosis	Number of Cases	Average Duration of Symptoms in Hours	Amount of Gas in Intestinal Tract	Degree of Distention of Small Bowel	Fluid Levels	"Thickening" of Bowel Wall	Visibility of Properitoneal Fat Line	Degree of Distention of Large Bowel
Early small bowel obstruction,† simple	7	15	++	++	+++	±	+++	±
Early small bowel obstruction, strangulated‡	8	18	++	++	++	++	++	±
Late small bowel obstruction,† simple	20	65	+++	+++	+++	++	+++	±
Late small bowel obstruction, strangulated	6	48	+++	+++	+++	+++	+	+
Appendicitis, perforated	7	56	+++	++	++	++	+	++
Peritonitis due to pelvic inflammatory disease	6	96	++	±	+	++	++	++
Peritonitis due to other causes	12	80	+++	++	++	++	++	++
Acute cholecystitis	3	32	++	+	+	+	++	++
Large bowel obstruction	9	112	+++	±	++	++	++	++++
Large bowel volvulus	4	114	++++	++	+++	++++	+	+++
Fecal impaction	5	(20-48) 33	++	++	+	±	+++	++

* Data on the other 13 cases are listed in table 3.

† Early obstruction is that observed within twenty-four hours of the onset of the symptoms; late obstruction, after that time.

‡ Strangulated obstruction is obstruction associated with partial or complete occlusion of the vascular supply of the involved segment of bowel; peritoneal exudate appears early in such cases, and prompt surgical intervention is imperative.

TABLE 3.—*Differential Diagnostic Findings in Thirteen Atypical Cases of Intestinal Obstruction and Paralytic Ileus* *

Diagnosis	Number of Cases	Average Duration of Symptoms in Hours	Amount of Gas in Intestinal Tract	Degree of Distention of Small Bowel	Fluid† Levels	"Thickening" of Bowel Wall	Visibility of Properitoneal Fat Line	Degree of Distention of Large Bowel
Acute enteritis	2	95	+++	+++	++	+++	+	+
Typhoid fever	1	192	+++	++	+++	±	+++	+
Acute obstruction, strangulated	2	30	0	0	0	0	++	0
Morphine addiction	1	96	+++	+	0	++	+++	++
Mesenteric thrombosis, colon	1	240	++++	0	?	++	+++	++++
Mesenteric thrombosis, ileum	1	72	++	++	++++	+	+++	+
Regional ileitis	1	1 yr.	++	+	?	++	+	++
Pyelitis	1	60	++	0	0	+	0	+
Chronic pelvic inflammatory disease	1	48	++	0	?	+	++	+
Gallstone impaction, duodenum‡	1	120	++++	0	?	+++	+	++++
Functional vomiting	1	48	++	0	?	+	+++	++

* The method of grading is the same as that followed in table 2.

† A question mark indicates that no upright or lateral decubitus roentgenogram was available to indicate the presence or absence of fluid levels.

‡ This condition was complicated by peritonitis and "secondary" ileus (note the duration, five days).

acute obstruction listed in table 3. We are unable to explain the absence of gaseous distention in these 2 cases. We did not find that the amount of gas in the stomach, if it was present at all, was of any significance.

Gaseous distention of the small intestine occurs in many different conditions. The mere presence of gas shadows in roentgenograms of the small bowel, unattended by significant distention of the lumen, is of little importance. It is well known that swallowed air passes readily into the small bowel when the person is in the recumbent or in the left lateral decubitus position.[6] However, when distention is present, accompanied by abdominal pain, nausea, vomiting and obstipation,

Fig. 1.—Roentgenograms taken in 2 cases of early obstruction of the small bowel, illustrating the difference in the apparent thickness of the bowel wall in cases of simple obstruction as compared with those of strangulated obstruction. *A* shows several dilated, gas-filled loops of jejunum with normal "wall thickness." The patient was a 42 year old woman, who had cramps and nausea for eighteen hours and vomiting for four hours. Operation showed ileal obstruction due to adhesions; there was no peritonitis. *B* shows several dilated, gas-filled loops of jejunum with abnormal "wall thickness" (i. e., peritoneal fluid). The patient was a man aged 53 years, who had pain, nausea and vomiting for twelve hours. Operation showed ileal obstruction due to an incarcerated left inguinal hernia; there were peritoneal exudate and infection.

mechanical or paralytic ileus is fairly certain to be present. If the symptoms are of less than forty-eight hours' duration, if fluid levels are present, if the bowel wall is not "thickened" (separated) by peritoneal

6. Van der Burg, L. W.: Over het elimineeren van darmgassen, storend voor de röntgendiagnostiek, Thesis, Bandoeing, Java, 1937.

exudate and if the properitoneal fat line [7] is evident, then acute mechanical obstruction should be suspected.

If apparent thickening of the bowel wall is seen (peritoneal exudate), with or without partial obscuration of the properitoneal fat line, the probable cause is either a strangulated intestinal obstruction or peritonitis with paralytic ileus. Significant distention of the large intestine is evidence of paralytic ileus. In cases in which the condition is of more than forty-eight hours' duration, these differential characteristics are lost, according to our experience; this is presumably due to peritoneal irritation and "secondary" ileus following long-standing obstruction from any cause.

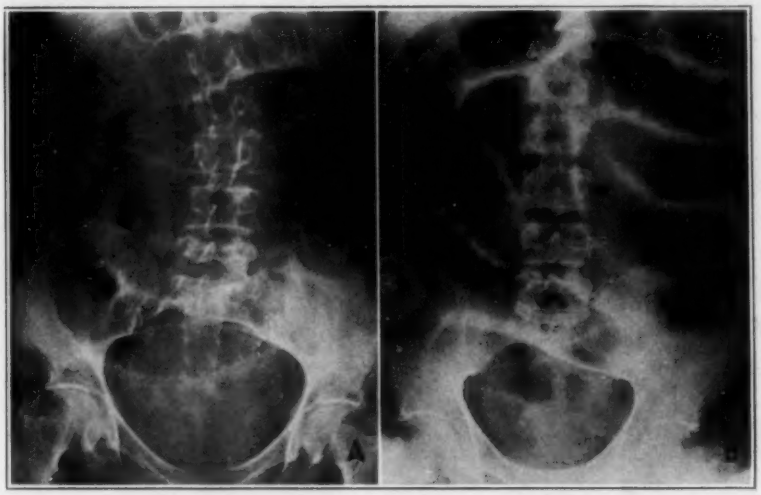

Fig. 2.—Roentgenograms taken in 2 cases of late obstruction of the small bowel, illustrating greater distention of the bowel as compared with the cases of earlier stages illustrated in figure 1. These cases also show the difference between nonstrangulated and strangulated obstruction. *A* shows several gas-dilated loops of small bowel with a small amount of peritoneal exudate. The patient, a woman aged 62 years, had cramps and vomiting for thirty-four hours. Operation showed ileal obstruction due to adhesions; there was no peritoneal infection. *B* shows several gas-dilated loops of jejunum separated by a large amount of peritoneal exudate. The patient, a man aged 46 years, had cramps, nausea and vomiting for two days; an enema elicited bloody stools. Operation showed ileocolic intussusception due to an ileal polyp; peritonitis was present.

We have learned to place much greater confidence in the presence of peritoneal exudate, as shown by apparent thickening of the bowel wall

7. The properitoneal fat line is the line of diminished density observed in the lateral portions of abdominal roentgenograms, mesial to the soft tissues of the abdominal wall; it lies in the area between the iliac crests and the lower ribs. Its obliteration is suggestive of peritonitis and is presumably due to edema of the fatty tissues (cf. the obliteration of the psoas margin in perinephric inflammation).

(that is, separation of adjacent loops of bowel), than in the obliteration of the properitoneal fat line, as an indication of the presence of peritoneal irritation, or peritonitis. The fat line was present in some of our cases of peritonitis of long standing, and was absent in a fair number of our cases in which no peritoneal exudate could be demonstrated. Occasionally, when two roentgenograms were made of the same patient at one examination, one of the roentgenograms showed the line clearly and the other showed no such shadow. When considered with other roentgenologic findings, however, the properitoneal fat line is often of definite assistance in diagnosis.

Gas was present in the colon in the majority of cases in this series, whether the distention was due to mechanical obstruction or to paralytic

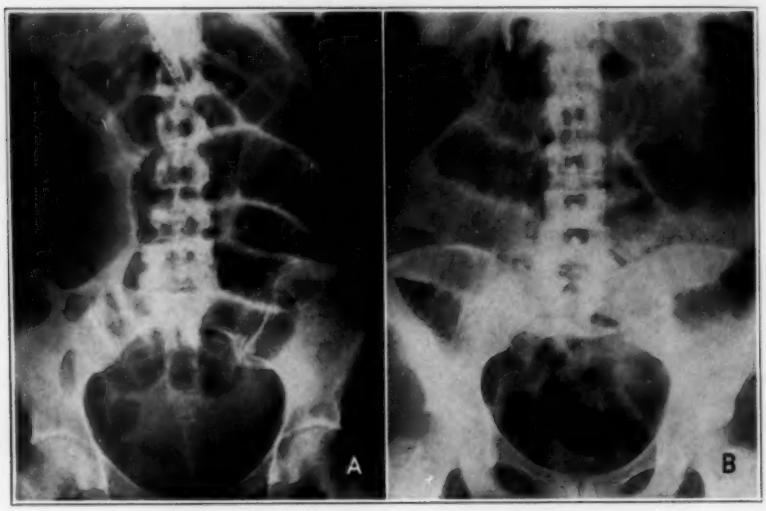

Fig. 3.—Roentgenograms taken in 2 cases of paralytic ileus, illustrating marked gaseous distention and moderate peritoneal exudate. *A* shows gas-dilated loops of small and large bowel and peritoneal exudate. The patient was a woman aged 30 years, who had nausea, vomiting, abdominal pain and diarrhea for three days. The clinical diagnosis was ruptured appendix with peritonitis. Conservative treatment was given and was followed by recovery. *B* shows gas-dilated loops of small and large bowel with some peritoneal exudate. The patient was a diabetic woman, aged 62 years, who had nausea, vomiting and abdominal pain for five days as well as some diarrhea. The clinical diagnosis was acute enteritis and diabetic acidosis. Conservative treatment was followed by recovery. Examination of the stools did not reveal Bacillus dysenteriae, Bacillus typhosus or Bacillus paratyphosus A or B.

ileus. Any considerable distention of the colon led us to suspect peritonitis or some other cause of paralytic ileus unless the condition was in a late stage (duration over forty-eight hours). The absence of fluid levels in roentgenograms made with a horizontal beam was, in our

experience, good evidence of the absence of true obstruction or paralysis of the bowel; for example, "dry" collections of gas are common accompaniments of such condition as pyelitis and ureteral colic. We tried to obtain roentgenograms with the patient in an upright position when his condition warranted; in other cases posteroanterior roentgenograms made with the patient in the left lateral decubitus position were satisfactory.

SUMMARY AND CONCLUSIONS

Roentgenographic findings in 100 proved cases of mechanical or paralytic ileus are presented in tabular form.

Early stages of acute mechanical intestinal obstruction due to adhesions or bands can often be differentiated roentgenologically from strangulated obstruction and from peritonitis.

Late stages of mechanical obstruction are frequently difficult to distinguish roentgenologically from paralytic ileus and from mesenteric thrombosis.

Consideration of the clinical history and findings is essential for the intelligent interpretation of abdominal roentgenograms in cases of suspected intestinal obstruction.

There is a small group of cases in which no roentgen evidence of intestinal obstruction is found, even though complete obstruction is present. For this reason a negative roentgenologic report must not preclude careful clinical observation of the patient, supplemented by repeated roentgenographic examinations at short intervals (about four hours), until a diagnosis is established.

REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.
LOS ANGELES
FRANK HINMAN, M.D.
SAN FRANCISCO
ALEXANDER VON LICHTENBERG, M.D.
BUDAPEST, HUNGARY
ALEXANDER B. HEPLER, M.D.
SEATTLE
ROBERT GUTIERREZ, M.D.
NEW YORK
GERSHOM J. THOMPSON, M.D.
AND
JAMES T. PRIESTLEY, M.D.
ROCHESTER, MINN.
EGON WILDBOLZ, M.D.
BERNE, SWITZERLAND
AND
VINCENT J. O'CONOR, M.D.
CHICAGO

KIDNEY

Surgical Technic.—Bonanome [1] stated that, although resection of the kidney is not a new type of intervention, it has within recent years received more attention as the result of improvements in its technic. Furthermore, the improvements that have been achieved in diagnosis have made it possible to recognize the precise indications for this operation.

Partial nephrectomy may be subdivided into two types: polar (renal amputation) and median (renal resection). Bonanome gave the name of renal resection to the latter only. On the basis of an illustrative case, he concluded that this operation is attended by no more dangers than is common nephrectomy and that it should be carried out whenever the proper indications are present. If the portion of kidney to be removed contains a cavity, as it did in the case cited, it is advisable first to open this cavity in order to learn the points at which the incisions should be made in the kidney for the resection.

During resection of the renal parenchyma the author has never observed such hemorrhages as might necessitate making compression

1. Bonanome, L.: Contributo alla resezione renale. Caso clinico, Urologia **6**:3-6 (March) 1939.

on the renal pedicle, but the surgeon should always bear in mind the possibility of such an occurrence. Small bleedings have always been controlled easily by use of hot compresses and by approximation of the sectioned flaps. In no case has it been necessary to have recourse to interposition of autoplastic or heteroplastic substances for hemostasis, nor has there been any secondary hemorrhage.

In Bonanome's opinion the surgeon should discard, whenever possible, the method of interposition of fatty or muscular tissues as a covering; for hemostasis it is unimportant, and for reconstruction it is nearly always enough to approximate the sectioned flaps if the surgeon bears this in mind during section.

It is desirable to bring the margins together by means of double catgut sutures that bite far into the capsule and parenchyma, as in the case cited. In this way it is possible to make much greater traction on the sutures in drawing the flaps together without their cutting the substance of the parenchyma. Furthermore, fewer sutures are required to reconstruct the kidney. The capsule is then sutured separately in addition. No fistula has ever resulted after performance of this operation by the author and his associates.

Mathé [1a] stated that clampless nephrectomy is the operation of choice in dealing with kidneys in which such conditions as ectopia, incomplete rotation and aberrant distribution of blood vessels are present, in dealing with horseshoe kidney and in those cases in which the surgeon is called on to remove a kidney destroyed by tuberculosis, pyohydronephrosis, formation of abscess or calculous disease. It is also indicated for removal of the hydronephrotic kidney, in which the elongated vessels readily lend themselves to clampless ligation.

Clampless nephrectomy is contraindicated for patients suffering from extensive perirenal fibrosis, for patients with kidneys with a short pedicle, for patients presenting extensive scar formation resulting from previous operations and in cases of renal tumor.

Mathé's technic calls for adequate exposure, careful dissection and meticulous manipulation of the renal blood vessels. Clampless nephrectomy is simplified and made safer by dissecting the pedicle free with a mounted cherry sponge and by utilizing a nontraumatizing curved mosquito forceps in order to place the ligature around the blood vessels that are to be ligated.

Clampless nephrectomy was successfully performed on 20 patients. Success depends on careful, cleancut dissection, which prevents injury to surrounding structures. It assures a more nearly perfect specimen, is accompanied by less shock and is followed by a smoother convalescence than is the case with other procedures.

1a. Mathé, C. P.: Clampless Nephrectomy, J. Urol. **42**:1135-1144 (Dec.) 1939.

Hess [2] discussed resection of the rib in renal operations, a procedure which he said he has been carrying out for twelve years. An incision is made in the skin over the twelfth rib; the rib is dissected free and is then resected from its attachment at the vertebra. The kidney, surrounded by Gerota's capsule, is then separated posteriorly as far as the pedicle. This is done with the surgeon's fingers, by finding the line of cleavage between Gerota's capsule and the transversalis fascia. Gerota's capsule is then opened on the posterior surface of the kidney, near the hilus, and the incision is enlarged with the fingers.

The advantages of the incision are (1) simplicity of operative exposure of the whole kidney and adrenal region with a relatively small incision; (2) protection of the iliohypogastric, ilioinguinal and intercostal nerves and vessels, preventing anesthesia of the lower abdominal quadrant; (3) less direct trauma to the muscles of the abdomen (which are always severely injured by all other incisions in the loin), preventing postoperative hernia, and (4) the fact that retraction is seldom necessary and, when it is, need not be very forceful.

Hydronephrosis.—Berkman and Priestley [3] described a symptom complex occasionally produced by unilateral uninfected hydronephrosis, which is characterized by a dull, aching, nonextending pain in the upper part of the abdomen. This pain is usually aggravated by activity of the patient in the erect posture and relieved by his reclining on the back, on the opposite side or, rarely, on the affected side. It is frequently accompanied by anorexia and nausea, sometimes severe, and occasionally by vomiting. Berkman and Priestley emphasized the importance of recognizing this symptom complex. Patients who present these complaints without apparent organic disease to explain their symptoms frequently may be considered neurotic, because physical examination, urinalysis and roentgen studies of the gastrointestinal tract, kidneys, ureters and bladder may reveal nothing abnormal. Intravenous urographic examination is the best method of confirming the suspicions which the patient's history may arouse. Treatment is surgical. The best type of surgical procedure to employ depends on the cause and nature of the hydronephrosis. Sixteen instances of the condition have been encountered, 4 of which are presented in detail.

Tumor.—Ostrum and Fetter [4] stated that advanced renal malignant disease frequently exists without symptoms referable to the organ of

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2. Hess, E.: Resection of the Rib in Renal Operations, J. Urol. **42**:943-949 (Dec.) 1939.

3. Berkman, J. M., and Priestley, J. T.: The "Position-Relief Syndrome" of Hydronephrosis, Minnesota Med. **22**:217-222 (April) 1939.

4. Ostrum, H. W., and Fetter, J. S.: Silent Nephroma, J. Urol. **43**:39-51 (Jan.) 1940.

origin but, rather, with symptoms pointing almost exclusively to sites of distant metastases.

The usual clinical triad of hematuria, pain and abdominal tumor is by no means essential to the focusing of clinical suspicion on the urinary tract. If any one of these three clinical manifestations is observed, "a uroradiographic study is indicated, provided a definite diagnosis is not otherwise forthcoming in due time."

When a malignant bone lesion is noted or suspected in the course of radiographic or roentgenoscopic examination, particularly in the aged, the urologist always should investigate the kidneys before concluding that the condition has been sufficiently studied.

The occurrence of even a single episode of gross or microscopic hematuria should always be noted with serious concern.

Maslow [5] reported 3 cases of Wilms's tumor, with the possible existence of a fourth, in children of the same family. All 4 children were normal, had been delivered at full term and apparently had been normal in every respect until they were taken ill. There were 2 boys and 2 girls, and their ages ranged from 13 months to 4 years. The left side was involved in 3 children; the right, in 1. Abdominal tumor was the presenting symptom in 3 cases, and the fourth child was brought to the hospital with symptoms of intestinal obstruction. Hematuria was present in 1 case. According to the mother, in 3 of the children the onset of abdominal enlargement was preceded by an acute condition: acute tonsillitis in the first, injury from a fall in the second and severe chickenpox in the third. One patient received no treatment at all; 1 was operated on with a diagnosis of ileus, and an inoperable Wilms tumor was found; 1 underwent nephrectomy and postoperative roentgen therapy, and 1 received preoperative roentgen therapy followed by nephrectomy and postoperative roentgen therapy.

Smyth [6] stated that not infrequently hypernephromas develop silently and that metastasis may be the first sign of the disease. He reported 2 cases. In both there was an absence of urinary symptoms, and in both the metastasis first drew attention to the disease. In 1 case a tumor which was not palpable infiltrated the kidney rapidly and caused widespread dissemination, whereas in the other case a slow, indolent type of growth gave rise to solitary metastasis.

Smyth discussed the two classifications of Foulds and Braasch: alveolar carcinoma, which is the more malignant type, and adenocarcinoma, which is the less malignant type. The clinical history of the

5. Maslow, L. A.: Wilms Tumor: Report of Three Cases and a Possible Fourth One in the Same Family, J. Urol. **43**:75-81 (Jan.) 1940.

6. Smyth, M. J.: Silent Hypernephromata, Brit. J. Surg. **27**:266-274 (Oct.) 1939.

less malignant type is sometimes remarkably prolonged. In some patients the disease has existed from twenty to forty years. One patient had had a palpable tumor for thirty years, and in another a growth was known to have existed for sixteen years.

Metastases may cause confusion, and in the absence of a biopsy investigation of the kidneys should not be forgotten. Smyth stated that evidence of only one metastasis should encourage the surgeon to undertake the double operation, since it may mean complete eradication of the disease.

Adams and Hunt [7] stated that Wilms's tumor of the kidney is the most common abdominal tumor in children.

The usual finding in cases of Wilms's tumor is an abdominal mass, frequently accompanied with loss of appetite, dilated superficial veins, vomiting and abdominal distress. Hematuria is rare. Some aspects of Wilms's tumor can be simulated by neoplasms of the adrenal gland, other retroperitoneal neoplasms, tumors of the liver and unusual congenital anomalies.

A reasonably accurate diagnosis should always precede heavy preoperative irradiation therapy. Radiosensitiveness is of no value in the differential diagnosis of Wilms's tumor.

Medulloblastoma of the adrenal gland is more radiosensitive than Wilms's tumor, and in certain cases of unverified Wilms's tumor in which the patients were reported cured by irradiation the tumor probably was medulloblastoma.

Preoperative irradiation followed by nephrectomy when practicable is advocated as the treatment of choice for Wilms's tumor.

Excretory urographic study after intramuscular injection of diodrast (a solution of 17 to 35 per cent 3,5-diiodo-4-pyridone-*N*-acetic acid and diethanolamine) is a safe and helpful diagnostic procedure in case of the existence of small or blocked veins and in the handling of uncooperative patients.

Tuberculosis.—Howard [8] discussed the management of the ureter in the presence of tuberculous lesions of the kidney. He wrote that he removes the kidney in the usual manner, freeing it of its pedicle, but that he does not cut the ureter. The kidney, still attached to the ureter, is pulled out from the lower angle of the wound. The wound is covered with an alcohol-soaked sponge, and the kidney is cut from the ureter, ½ inch (1.27 cm.) of the ureter being left protruding. A catheter or a glass connecting tip is introduced into the lumen and tied. This facili-

7. Adams, P. S., and Hunt, H. B.: Differential Diagnosis of Wilms' Tumor Assisted by Intramuscular Urography, J. Urol. **42**:689-708 (Nov.) 1939.

8. Howard, T. L.: The Management of the Ureter in Tuberculous Lesions of the Kidney, J. Urol. **42**:1003-1009 (Dec.) 1939.

tates treatment of the ureter and bladder by instillations or irrigations with any antiseptic medium or solution.

Henline,[9] in discussing Howard's paper, said that the question of proper treatment of the tuberculous infected ureter after nephrectomy is still unsettled. Formation of draining sinuses has occurred after nephrectomy for tuberculosis in 67.7 per cent of 97 cases recently studied.

Most urologists believe that these sinuses result from infection in the stump of the ureter. However, some believe that the perirenal fat is already infected when tuberculosis of the kidney is discovered or becomes infected from manipulation during nephrectomy and that the wound will break down and form a sinus regardless of the treatment of the cut end of the ureter.

Following Howard's suggestion, Henline, in performing seven nephrectomies in 7 cases of tuberculous kidney, clamped and tied the pedicle, permitting the kidney to remain attached to the ureter until the entire wound was sutured. The ureter, with the kidney attached, emerged at the anterior angle of the wound.

The wound remained closed in 4 of the 7 patients, except at the site of the ureteral transplant to the skin. Two of the four ureteral wounds healed in fifty-four and eighty-three days respectively, and at the time of Henline's discussion the other two were still draining, two hundred and ten and seventy-five days respectively after operation.

The renal wounds of the remaining 3 patients opened, those of 2 closing in one hundred and eighty-six and one hundred and eight days respectively and the third continuing to drain eighty-five days after operation. Four ureteral stumps remained viable and were removed in an average of nineteen days after operation, whereas three of the stumps became necrotic and sloughed in sixteen days. No catheter or glass connecting tip was placed in any of these ureters.

Mycobacterium tuberculosis was discovered in the urine of each of these patients. The vesical symptoms had completely disappeared in 4 patients at the time Henline spoke and were much improved in 2, and 1 patient showed little symptomatic change.

Henline stated that the results achieved in treating these few patients by merely transplanting the ureter in the lowest angle of the wound have not reduced the morbidity following this operation as much as he had hoped.

Stone.—Priestley[10] discussed the treatment for unilateral and bilateral stag-horn renal calculi.

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9. Henline, R. B., in discussion on Howard,[8] p. 1033.

10. Priestley, J. T.: Treatment for Unilateral and Bilateral, Stag-Horn Renal Calculi, J. Urol. **42**:933-942 (Dec.) 1939.

Large, branched renal calculi often do not produce severe pain or other symptoms which direct attention to the urinary tract. Despite this fact, stones of this type, whether unilateral or bilateral, cause progressive renal damage. When a unilateral stag-horn calculus is present, the chance of removing the stone and preserving a functioning kidney is gradually reduced the longer operation is postponed. When bilateral stag-horn stones are present, the outcome under medical management is almost invariably progressive renal damage until renal insufficiency ensues. Stag-horn stones can be removed from the kidney when renal function is adequate, with a low operative risk and with the expectation of favorable late results in the majority of cases. Early operation for unilateral or bilateral branched renal stones usually seems advisable.

If renal function is diminished, a period of appropriate preoperative preparation is essential. The details of surgical management will vary somewhat in each individual case. Pelviolithotomy, if feasible, is the operation of choice; if not, nephrolithotomy is required. The insertion of a nephrostomy tube at the time of operation is desirable. Any obstructive factor at the ureteropelvic juncture should be relieved if the condition of the kidney and of the patient warrants such a procedure.

Gonzalez [11] observed that it is common for patients who have undergone conservative operation for septic stones of the kidney or of the ureter to manifest no improvement in their functional condition between entering and leaving the hospital. This led him to watch the mechanical and functional results for a longer period. Patients returned for troubles which could not be attributed to a return of lithiasis but were referable to lesions caused by the stone from the time of onset of the disease.

Seven patients were studied for an entire year after leaving the hospital. The time that these patients had suffered from symptoms of lithiasis before their operations ranged from two to twenty-six years. Anatomic and functional changes had occurred in every case, but they were worst in those patients who had suffered longest before coming to operation. The anatomic changes consisted chiefly of dilatation, especially when ureteral stones had been present. In such cases the lesions were even more pronounced and persistent, without modification, after operative treatment. In all there was infection. In every case there was deficiency of renal function. Examination showed that the function remains stationary or even becomes worse after conservative treatment (pyelotomy, ureterostomy). Surgical treatment, then, has not arrested the progressive course of functional changes. It is, therefore, evident that complete restoration must be considered improbable.

11. Gonzalez, R.: Étude de la fonction rénale après les opérations conservatrices de la lithiase réno-urétérale, J. d'urol. **47**:110-127 (Feb.) 1939.

The importance of these changes depends on three factors: (1) the stone and its localization, (2) the time elapsed and (3) presence of infectious processes. What has happened is that, in replacing the damaged tissue, connective tissue has not only taken the place of normal tissue but has invaded the latter over a greater or lesser tract, according to the age of the lesions. This applies to changes in the ureter, pelvis and calices and explains why urologists cannot expect anatomic forms and histologic structures to regenerate. After these anatomic changes, the modifications of renal function depend on innumerable factors, the behavior of which is too complex to be determined. Gonzalez concluded in agreement with Hinman that the changes following complete obstruction of the ureters are alike in all species proportional to the degree of the lesion and that compensatory hypertrophy of the opposite kidney is progressive and becomes anatomically complete between the thirtieth and the fortieth day, although the functional reserve has not yet attained its maximal power.

He thus deduced that an obstacle causing changes in the renal parenchyma causes proportional hypertrophy in the opposite kidney. Animal experiments show that the renal parenchyma that is least injured is most likely to receive physiologic stimulants which control function and reparation. They show that repair of lesions is in inverse proportion to the time the lesions have been evolving. In cases in which the opposite kidney remains sound, this kidney alone is capable of meeting the needs of the situation. This explains why lesions of the diseased kidney remain stationary.

In clinical treatment, however, difficulties are met in appreciating the exact form of the renal activity, and the general ignorance of the intimate mechanism of renal function becomes apparent. It is evident that more study is necessary for an understanding of the upper part of the urinary apparatus in cases of renal stone, and also of the ureter, to determine the degree of the changes present. Prognosis must be reserved even after examination of the lesions. Treatment will depend on the ability of the urologist to arrive at a correct diagnosis with reference to the nature and extent of these lesions.

Birdsall [12] discussed the incidence of obstruction of the urinary tract in the formation of renal calculus. The subject matter of the paper comprises a study of 150 cases of renal calculi and 61 cases of ureteral calculi, totaling 211 cases of lithiasis of the upper portion of the urinary tract.

Nephroptosis with angulation of the ureter was the most frequently encountered type of obstruction of the urinary tract in association with

12. Birdsall, J. C.: The Incidence of Urinary Tract Obstruction in Renal Calculus Formation, J. Urol. **42**:917-932 (Dec.) 1939.

which renal and ureteral calculi were found. In many cases comparatively small calculi were demonstrated by pyelographic studies to be situated in the minor calices, giving evidence of having been formed on the renal papillae. Many other types of obstruction, such as bands, vessels, stricture of the ureter and various types of anomalies, such as renal duplication, crossed ectopia, horseshoe kidneys and polycystic disease, were the underlying cause of hydronephrosis, stasis of urine and formation of calculus.

As a result of pyelographic studies, hydronephrosis was found to be present in 179, pyonephrosis in 23 and pyelonephritis in 9 cases. Infection also played an important role and was found in 168 cases, in 43 of which ureteral calculus was present and in 125 of which renal calculus was present.

Surraco [13] described a technic for extraction of large calculi from the kidney, in which he makes use of extrinsic pyelotomy instead of nephrotomy. His method takes advantage of the anatomic relations of the renal sinus, the pelvic cavities and the retropyelic vessels, all of which he discussed. The aim of his method is "to expose widely the posterior surface of the intrasinusal pelvis and that of the primary calices" for the purpose of intrarenal exploration. The operation consists of five stages, illustrated in Surraco's paper by appropriate drawings. It begins like any decapsulation procedure, a flap of capsule being cut in the form of an arc. This curved flap then corresponds to a sector of the posterior wall near the renal sinus. It is easy to free the capsule into the renal sinus, separating it from the posterior wall of this sinus. It is likewise easy to separate the retropyelic vessels at the same time with the capsule, to which they remain adherent, thus leaving the posterior surface of the cavities of the pelvicalicular system completely free. The flap of capsule is then cut at its end, section being continued as far as the margin of the renal sinus. Then in front of the retropyelic veins, which have been brought down by a series of strokes, the flap is cut as far as the interior of the renal sinus, whereupon the pelvis becomes fully exposed, its posterior surface as well as that of the primary calices being in full view.

An incision along the axis of the pelvis will provide easy access to the calices. Then by digital exploration the mouth of each calix can be found, dilated and penetrated to its apex with bimanual palpation. The finger, introduced into the calices, discovers all irregularities and foreign bodies that may lie within them, extracts them and executes all necessary maneuvers.

By means of this procedure it is possible to extract all coralliform stones, no matter how complicated their formation may be, proceeding

13. Surraco, L. A.: L'extraction des gros calculs du rein; pyélotomie postérieure étendue pelvi-caliculaire, J. d'urol. **48**:217-223 (Sept.) 1939.

separately in each calix, and when there are small fragments, the exploring finger within the canaliculi can perform a miniature nephrotomy to help in the extraction.

This method, therefore, permits the surgeon to explore with ease all the renal cavities, by double palpation, to discover every change which may exist within diverticular cavities, to remove stones of all sorts, even those with very complex arborizations, to make with the exploring finger complementary nephrotomies and to carry out ample drainage of all intrarenal cavities.

Rupture.—Peacock [14] reported a series of cases and stated that rupture of the kidney may be produced by apparently mild trauma. Diseased kidneys are more prone to rupture than healthy ones. Automobile accidents constitute the greatest causative agent. Hematuria, localized pain in the loin, tumefaction and shock are the commonest symptoms. Palpation and excretory urographic study are the best diagnostic aids. Expectant treatment is superior to immediate operation.

Trauma.—Farman [15] stated that the incidence of traumatic rupture of the kidney is low but that such injuries appear to be on the increase, mainly because of modern traffic accidents. Farman reported 3 cases of total rupture of the kidney. In 2 the rupture was the result of an automobile accident, and in 1 it followed a football injury. Nephrectomy was performed in all 3 cases, with 1 death.

It is necessary to determine the extent and type of injury and the expected course. Aside from the history of trauma, the presence of hematuria, pain in the renal region and some degree of shock, the physical observations are important in determining the severity of renal lesions. Opinion differs as to the relative value and danger of cystoscopic, pyelographic and intravenous urographic examination. The argument against cystoscopic and pyelographic procedure in cases of renal injury is the possibility of introducing infection into a fertile bed of traumatized tissue and of increasing the hemorrhage. Some urologists advocate intravenous urographic examination, but the disadvantage in its use is that the roentgen findings cannot be depended on to portray the actual traumatic lesion, because the secretory powers of the kidney are reduced or inhibited by trauma. Experimental and clinical trial has proved in general that retrograde pyelographic study is the more useful and dependable procedure for the early diagnosis of severe injuries to the kidney.

In all cases in which there is no severe bleeding from the kidney and no demonstrable injury to other organs, a waiting policy is the

14. Peacock, A. H.: Rupture of the Kidney, West. J. Surg. **48**:129-134 (March) 1940.

15. Farman, F.: Diagnostic and Operative Factors in Traumatic Rupture of the Kidney, J. A. M. A. **114**:210-216 (Jan. 20) 1940.

procedure of choice. Rest in bed, application of an ice bag to the side and administration of morphine constitute the treatment to be employed. Urologists are not at all in unanimous agreement as to the indications for operative intervention, mainly, in Farman's opinion, because of the difficulties of correct interpretation of clinical and urographic data. Early surgical exploration and repair are advocated by many because of the high mortality rate of rupture of the kidney. Nephrectomy is indicated by extensive destruction of tissue, multiple deep lacerations, injury to the pedicle, irreparable tears of the pelvis or ureter or persistent hemorrhage.

Some injuries of the kidney treated by expectant or conservative surgical methods require secondary nephrectomy if complicating sequelae follow, such as persistence of a urinary sinus, formation of a perirenal abscess or incapacitating chronic pyelonephritis.

Harrison [16] reported 27 cases in which patients suffered from renal trauma. In each instance injury had been caused by direct application of force over the kidney.

Hematuria is the cardinal sign of injury to the kidney of a patient who has recently sustained an accident.

Conservative treatment yields good results. There is a tendency for spontaneous improvement to occur, because of the processes of natural repair. The absolute indications for operation are persistent hemorrhage, extravasation of urine and renal infection. There was no mortality in Harrison's series.

Because of the possibility that congenital or acquired lesions of the kidney may antedate the trauma, thorough studies of the uninjured kidney as well as of the traumatized organ must precede operation.

Prather [17] evaluated certain observations and diagnostic procedures in the care of patients having renal injuries, differentiating those cases in which palliative measures will suffice from those in which surgical intervention is necessary.

The important clinical points which appear to place the condition in a group known as "contusions of the kidney needing only palliative treatment" are:

1. No evidence of shock (90 per cent of cases).

2. No decrease in blood pressure during the first forty-eight hours of hospitalization.

3. No increase in pulse rate in 90 per cent during the first two days in the hospital.

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16. Harrison, J. H.: Trauma to the Kidney, Surg., Gynec. & Obst. **70**:93-104 (Jan.) 1940.

17. Prather, G. C.: Traumatic Conditions of the Kidney: Clinical Observations, J. A. M. A. **114**:207-210 (Jan. 20) 1940.

4. No increase in tenderness of the flank or of the abdomen during a forty-eight hour period after admission to the hospital.

5. Visualization of the injured kidney in a high percentage of cases, although secretion of dye injected intravenously may be delayed or diminished.

For those patients who have true rupture of the kidney and who do not die immediately from shock or hemorrhage, the following points seem pertinent. The most important clinical observation, which should be made by the same physician, is frequent examination for increasing tenderness and spasm in the lower abdominal quadrant of the injured side and evidence of spasm of the psoas muscles as evidenced by voluntary flexion of the hip. These features, Prather stated, indicate perirenal hemorrhage or extravasation of urine and are present even before there is any change in pulse rate or blood pressure. Use of intravenous pyelographic measures has been Prather's routine. Lack of visualization of the injured kidney is important and indicates the presence of a pathologic process requiring surgical treatment. Visualization of the kidney by means of intravenous pyelographic study does not rule out injury deserving surgical treatment. The choice between nephrectomy versus surgical repair of the injured kidney must be left to the experience and discretion of the operator. The condition of 1 patient who had traumatic severance of the renal pedicle and who lived for four days is described. Microscopic examination of the kidney of this patient indicated general infarction, but a thin rim of viable cortical tissue was present to a depth of 1 mm. just below the renal capsule, apparently kept alive by capsular vessels.

Perinephritic Abscess.—Vergoz and Lenck[18] made a study of anterior perinephritic phlegmon, with special reference to diagnosis and treatment of the condition. The diagnosis is particularly difficult because of the deep localization of such an abscess and because of the deceptiveness of its symptoms, which frequently cause it to be mistaken for retrocecal appendicitis and other suppurative abdominal conditions. Its relative rarity in comparison to the classic posterior perinephritic abscess also misleads, so that the diagnosis is most frequently made only at operation. A history of furunculosis, panaris or traumatism, is of importance in directing the diagnosis toward perinephritic abscess, and roentgen examination may then confirm its anterior localization. Excessive elevation of the dome of the diaphragm and its immobility during respiration are signs that have been pointed out by certain authors.

Intravenous urographic study, especially, may show the contours of a tumor and its relation to the kidney.

18. Vergoz and Lenck: Du phlegmon périnéphrétique antérieur, J. d'urol. **47**: 369-394 (May) 1939.

When the diagnosis cannot be made beyond the fact of the presence of an inflammatory tumor beneath the liver or near that organ and yet the possibility of an anterior perinephritic abscess is thought of, the only proper approach is the anterior route, with use of a transverse incision such as is made for surgical conditions of the liver and bile ducts. Exploration will then reveal the subperitoneal lesion in the region deep below the liver, where the posterior parietal serosa will be found to be red and edematous, with or without subjacent suppuration. The surgeon may then follow either of two courses: (1) closure of the peritoneal cavity, prolongation of the transverse incision toward the lumbar region and attack on the lesion by the subperitoneal route and by separation of the serosa (Bazy's method) or (2) walling off of the subhepatic region carefully with compresses and direct incision into the purulent collection. The second method is preferred by the authors as being simpler for patients already toxic from the effects of the abscess. In such cases a counterincision must be made in the lumbar region for drainage by gravity, while a Mikulicz drain (anterior) protects the peritoneum.

When the diagnosis of perinephritic abscess has been made but the location is uncertain, intervention should be made by the lumbar route. When this reveals only diffuse inflammatory edema, without the least sign of a purulent collection, the surgeon should never under any circumstances try to reach the anterior surface of the kidney with the finger and so gain access to the abscess; the danger to the peritoneum in such a procedure is too great. He should, rather, perform débridement of the internal lip of the lumbar incision and then make at its upper end an incision perpendicular to the primary incision; the peritoneum is thus separated and pushed back, and the prerenal suppurating cavity is opened. The surgeon can then easily transform the lumbar route into a lumboabdominal route, making it possible to reach with certainty the external margin of the kidney and its anterior aspect without touching the organ and without exteriorizing it.

When the diagnosis is correctly made before operation, the surgeon should strictly avoid the classic lumbar route, since it exposes only the lower part of the convex border of the kidney, and attempts made in this way to reach the upper pole are attended by great danger. The proper approach is the paraperitoneal route, with use of the anterior transverse incision of Bazy; this not only offers a more convenient position of the subject but leads directly to the anterior surface of the kidney and easily permits exploration of its entire contour.

The authors presented abstracts of 15 cases collected from the literature, to which they added 1 case of their own.

Gumma.—Hunter [19] reported a case of gumma of the kidney. The patient was a 53 year old man who had lost 25 pounds (11 Kg.) in the previous two years. The patient readily recovered after nephrectomy. The kidney weighed 2,265 Gm. The ureter was thickened and dilated. On section a lobulated, grayish yellow, extremely mottled, relief-map-like cut surface presented, with large, lobulated grayish yellow masses of the consistency of a myoma situated about the cortical portion of the tumor, while the central portion had a more grayish white, somewhat mottled fibrotic appearance. There was almost complete replacement of the renal parenchyma by the growth, which, generally speaking, was fairly well encompassed within the capsule except at the lower anterior pole, where it seemed to infiltrate the peritoneum and the perirenal fat. At the lower pole there was a cyst the size of a hen's egg, filled with a brownish yellow fluid rich in cholesterol crystals; the calices were markedly distorted, the superior one appearing rather dilated. The perivascular infiltrations, diffuse and focal infiltrations consisting chiefly of lymphocytes but also of numerous plasma cells, were seen throughout, and the picture seemed unquestionably that of a gummatous process.

Large syphilitic gummatous tumors are rare, and they are seldom diagnosed before operation. Microscopically, the lesion shows lymphocytic infiltration of plasma cells, with portions of necrosis and proliferation of connective tissue. It is not limited to the kidney but tends to infiltrate adjacent structures.

Atrophy.—Marion [20] defined an atrophic kidney as a kidney which, for any reason, is of reduced size, is very different from the normal kidney and, as a rule, has an anatomic constitution that is equally abnormal. Atrophic kidney may be congenital or acquired.

When congenital, the atrophy constitutes an actual malformation, comparable to the absence of a kidney. Congenital atrophic kidney represents an arrest of development during embryonic life. The kidney varies in size from that of a pea to that of an apricot. It is by study of the pelvis and calices that the urologist can determine whether the condition is congenital or acquired. In congenital conditions these excretory structures are never normal in their arrangement, being reduced either in size (barring hydronephrosis) or in number. The internal arrangements are, however, very variable; the parenchyma may be wholly normal, or it may be normal in portions, with sudden transition to fibrous tissue; or, again, there may be inflammatory or sclerotic lesions. In some cases the renal mass is composed entirely of excretory tubules, with entire absence of glomeruli.

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19. Hunter, A. W.: Gumma of Kidney, J. Urol. **42**:1176-1178 (Dec.) 1939.
20. Marion, G.: Reins atrophiques, J. d'urol. **47**:5-24 (Jan.) 1939.

Acquired atrophy, which is much more frequent, is caused by either infection or infarct. In nearly all cases it is caused by the former. The infection may be simple chronic pyelonephritis, or it may be referable to the presence of a foreign body (calculus or an intrarenal drain). It is never produced by tuberculosis unless some common infection is associated therewith. Atrophy caused by infarct is generally partial, for when an infarct is produced by obliteration of the great vessels surgical intervention is, as a rule, very prompt. In cases of total acquired atrophy, in addition to diminished size of the organ, the surface presents furrows, and on section the parenchyma is markedly diminished in thickness and is irregular both in surface and in color. Histologic examination reveals destruction of the normal elements of the kidney.

These atrophic kidneys frequently are absolutely silent, with no symptoms to indicate their presence. When symptoms do appear, there is nothing characteristic about them. The diagnosis is made in some cases by roentgenogram, which shows the presence of a stone, after which the atrophy is revealed at operation. In other cases the results of separate catheterization of the two ureters will give the required information; in such cases the atrophic kidney will betray its presence by deficient function as compared with the other kidney, especially with reference to the amount of urine excreted. The results of catheterization, taken together with the pyelogram, usually will be sufficient to confirm the diagnosis. Acquired atrophy will be recognized by renal deficiency associated with an absolutely normal pyelogram, whereas congenital atrophy will exhibit renal deficiency associated with a tiny pelvis and a diminished number of calices, in some cases only a single calix being present.

The prognosis is without gravity in itself, but, since a kidney of this type causes a condition equivalent to complete absence of a kidney, its presence is of greatest importance when a decision is to be made with reference to the other kidney, contraindicating its removal under any circumstances. Treatment consists in removal of the atrophic kidney if it gives any symptoms that are painful. If it continues to be silent, it may safely remain in its place indefinitely.

URETER

Calculus.—Thompson and Kibler [21] stated that ureteral calculi will pass spontaneously in about one third of the patients encountered; for approximately the same number, transurethral methods of extraction are justified and advisable; for the remaining third, ureterolithotomy or some other open surgical method seems best.

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21. Thompson, G. J., and Kibler, J. M.: Treatment of Ureteral Calculus, with Particular Reference to Transurethral Manipulation, J. A. M. A. **114**:6-11 (Jan. 6) 1940.

Ureteral stone extractors, if carefully used, will be of distinct aid in removing the stone at the time of manipulation. If the condition is suitable for the use of a metallic stone extractor, this instrument will readily enter the ureter and quickly engage the stone. Repeated attempts to engage the stone should be avoided, for they will usually result in ureteral trauma and lead to complications.

The morbidity following proper transurethral methods is slight, and the mortality is extremely low.

In the large majority of cases the opinion of a urologist should be obtained before a decision is made as to the course of treatment for a patient who has ureteral calculus.

Alyea [22] said that overemphasis has been placed on the invention of special instruments for the extraction of ureteral calculi and that perhaps the simplest, safest and most efficient methods have been overlooked. He stated the opinion that the multiple catheter method is both efficient and safe; it includes the principles of dilation, lubrication of the ureter and grasping of the stone in the mesh of twisted catheters. To this technic Alyea added the idea of continuous constant traction on the engaged calculus, followed by relaxation of the ureter by production of spinal anesthesia at the time of extraction. Once the stone is caught, constant traction is obtained by means of rubber bands taped to the twisted catheters and attached to a perineal traction cage. Olive oil is injected through the catheters several times, and, if the stone has not come out in twelve to twenty-four hours, spinal anesthesia is produced and the catheters are withdrawn. Many of the larger stones have been extracted in this manner. An objection often raised to cystoscopic removal is that the calculus remaining in the lower part of the ureter for some time causes irreparable damage to the kidney. Many cases have been observed in Alyea's clinic which disprove this contention. In a series of 400 cases of ureteral stone recorded at the clinic, the stones in 71 per cent were removed cystoscopically, and the mortality was zero in these 296 cases. Alyea said that he has used the various ureteral scissors, fulguration fins and the like for cutting the ureteral meatus. The Collings knife used through a panendoscope probably is the most satisfactory. It is introduced and turned so that the blade points anteriorly. After the intravesical portion of the ureter has been elevated with the blade, the surgical cutting current is touched, and the knife cuts through quickly. The surgeon is sure not to cut too deeply with this method. It is remarkable how meatotomy may start stones moving even though they may be 2 or 3 cm. from this region; Alyea stated that he has seen this occur many times.

22. Alyea, E. P., in discussion on Thompson and Kibler.[21]

Bumpus [23] stated that the question of what method shall be used in the treatment of calculi in the ureter has much in common with the question of what method shall be employed in treating benign prostatic hypertrophy. With both conditions the urologist's judgment is often unduly influenced by the desire of the patient to avoid a major surgical procedure. Bumpus expressed doubt that this state of affairs ever occurs more frequently than in the treatment of stones in the ureter. It is imperative to acquaint the patient with the possibilities of serious complications occurring as a result of manipulative procedures and to obtain his consent for immediate major surgical intervention should such complications occur. Such complications result from three causes. The first and most important is urinary obstruction; the second, ureteral trauma with its associated periureteritis, and the third (and least frequent), perforation. The possibility of occurrence of any of these three complications is minimized by avoiding the use of steel instruments and employing only catheters for manipulative procedures. The catheters insure the continued passage of urine if obstruction should occur. They produce the least amount of trauma, and it is difficult if not impossible to produce ureteral perforation with them. They have, moreover, the added advantage of being readily accessible for removal singly if the manipulator is unsuccessful, whereas, in the case of the mechanical instruments, if a stone gets caught crosswise neither the instrument nor the stone can be recovered without resort to some major surgical procedure.

Foley [24] stated that the decision between expectant treatment and manipulation or open operation in the case of a stone in the lumbar portion of the ureter presents an entirely different problem from that involved in the same decision in the case of a stone in the pelvic portion of the ureter. Pelvic ureterotomy is always a rather formidable procedure, beset by the usual hazards of major surgical operations. Accordingly, when the stone is situated in the pelvic portion of the ureter, a major operation of this sort usually should be avoided in favor of expectant treatment and manipulation. This is not the case when the stone is in the lumbar portion of the ureter. The usual form of lumbar ureterotomy is also distinctly a major operation, but it can and should be almost a minor one. When the choice is between this improved form of lumbar ureterotomy or expectant treatment and manipulation, there is in most cases very little to recommend the latter. The choice between expectant treatment and manipulation or open operation should be dictated by only one thing: the welfare of the patient. To attain this, the surgeon must consider the risk of mortality,

23. Bumpus, H. C., Jr., in discussion on Thompson and Kibler.[21]
24. Foley, F. E. B., in discussion on Thompson and Kibler.[21]

the risk of morbidity (irreparable pathologic change), the period of disability and the discomfort to be endured. In respect to all these, when the stone is first discovered in the lumbar portion of the ureter, the advantage lies entirely with a new form of lumbar ureterotomy devised by Foley and not with expectant treatment and manipulation. When a stone or anything of truly minute size is first discovered in the lumbar portion of the ureter, the patient's welfare will be served best by its immediate removal by this method of open operation. In such cases it is no trouble to start expectant treatment and manipulation, but how much trouble will ensue before success or failure results is another question. The patient will be obliged to endure at least a few attacks of colic. One or two or even three or four cystoscopic manipulations may be necessary, and they are a real hardship to the patient.

O'Conor [25] stated that the success of lumbar ureterotomy depends on the fact that the stone remains in that portion of the upper part of the ureter which it occupied before the incision was made. Some 20 per cent of these "upper ureteral calculi" will ascend to the upper part of the ureter or to the renal pelvis after the patient has been anesthetized, especially with spinal anesthesia, and with use of any degree of the Trendelenburg position. This same change of position has occurred no matter what position the patient has assumed on the operating table.

Lazarus [26] stated that the use of extract of insulin-free pancreatic tissue for three years has convinced him that this substance possesses distinct merit as an aid in the treatment of ureteral obstruction resulting from spasm, which frequently accompanies infection caused by calculi, and ureteral occlusions accompanying both functional and inflammatory strictures of the ureter. It has also proved of value in the treatment of postcystoscopic renal colic. The use of pancreatic substance (Grant), while it possesses all the merits of insulin-free tissue extract no. 568, has the distinct advantage of causing no pain at the site of the injection. To obtain the maximal benefit of the substance, ureteral catheterization should be instituted five minutes after its injection. Systemic reactions have not been observed in any of the cases in which it was employed. The most likely mode of action of this preparation in relieving spasm of the ureteral musculature is its neutralizing effect on the pressor action of epinephrine, as was suggested by Wolffe.

Ureterovaginal Fistula.—Ockerblad and Carlson [27] reported 5 cases of ureterovaginal fistula, in 4 of which the condition was caused by pelvic

25. O'Conor, V. J., in discussion on Thompson and Kibler.[21]

26. Lazarus, J. A.: Further Observations on Use of Insulin-Free Pancreatic Tissue Extract as an Aid in Cystoscopic Treatment of Impacted Ureteral Calculi and Spastic Occlusion of Ureter, J. Urol. **43**:102-107 (Jan.) 1940.

27. Ockerblad, N. F., and Carlson, H. E.: Surgical Treatment of Uretero-Vaginal Fistula, J. Urol. **42**:263-268 (Aug.) 1939.

operations. In the fifth it was referable to a ureteral calculus which had become impacted in the terminal 5 cm. of the left ureter and which followed a very unusual course by eroding through into the vagina.

A survey of the literature reveals scores of cases. The cure is still either reimplantation or nephrectomy. Reimplantation is done when possible, and nephrectomy is resorted to when the kidney is badly infected. Ockerblad and Carlson expressed disagreement with the opinion expressed by European writers that this operation is useless and that the end result is destruction of the kidney. There have been numerous cases in which the patient has lived longer than ten years in good health. They stated that to leave a part of a kidney which is healthy and not infected is much better than not to leave any kidney.

Patton [28] reported 16 cases of ureterovaginal fistula.

The importance of early investigation is stressed, with application of appropriate therapeutic measures in an effort to preserve the kidney.

A thorough urologic study is essential in every instance of leakage of urine through the vagina, even when a vesicovaginal or urethrovaginal fistula is obviously present.

The type of therapy to be applied to ureterovaginal fistula should be determined only after careful study and should be directed primarily toward preservation of renal function and reestablishment of the urinary channel to approximately its normal state. Nephrectomy should be reserved for the irreparably damaged kidney or as a measure of last resort.

Dilation should be the first procedure. In the event of failure, ureteroureteral anastomosis is the method of choice for high ureteral injuries, and reimplantation into the bladder is the method of choice for low ureteral injuries.

Patton described a method of reimplantation of the ureter into the bladder through the intramural portion of the ureter which reproduces the normal, and it should be applicable in a definite percentage of cases.

Transplantation.—Hess [29] stated that transplantation of the ureters into the bowel as an operative procedure should be considered only when a condition exists which makes life so miserable that death is usually to be preferred. The operation, even with the simplest efficient technic in the hands of the most skilful surgeons, is not without a very high mortality and morbidity. It is rarely indicated in cases of cancer of the bladder and vesicovaginal fistula. It is more frequently indicated for

28. Patton, J. F.: Ureterovaginal Fistula: A New Method of Reimplantation of the Ureter into the Bladder, J. Urol. **42**:1021-1032 (Dec.) 1939.

29. Hess, E.: Transplantation of the Ureters, Am. J. Surg. **45**:479-498 (Sept.) 1939.

the contracted bladder that has resulted from the healing of tuberculous cystitis, and with this class of condition there results a low mortality, with satisfactory symptomatic results. The procedure is also indicated in cases of intractable and incurable interstitial cystitis. It is a valuable procedure in cases of exstrophy of the bladder and epispadias but should never be used for exstrophy in the adult patient without a complete explanation to the patient of both its mortality and its morbidity, and it should be an operation elected by the patient.

Dilatation.—In a study of the ureteral dilatation of pregnancy, van Wagenen and Jenkins [30] stated that excretory urographic studies have shown that dilatation of the upper portion of the urinary tract occurs in the pregnant rhesus monkey.

Of the 6 pregnancies with which pyeloureteral dilatation was present, 1 was allowed to proceed without interruption, and the markedly dilated urinary tract returned to normal in seven days.

In 3 instances fetuses were removed after the dilatation had reached a high degree, and the dilatation was sustained or increased during the time the placenta remained in situ. After expulsion of the placenta the dilatation of the ureters always decreased, returning to normal size in every case in which the course was uncomplicated by infections.

The most convincing data concerning the primary importance of the hormonal influences of pregnancy in bringing about dilatation were those concerning 2 pregnancies in which the fetuses were removed on the seventy-fourth and the seventy-first day of gestation respectively. In the first animal beginning ureteral dilatation was found in the latter half of the fifth month, fifty-nine days after removal of the fetus. This dilatation increased considerably during the sixth month. The placenta was expelled on the one hundred and sixty-fourth day of gestation, after which dilatation regressed. In the second animal dilatation appeared only in the sixth month of pregnancy, eighty-one days after removal of the fetus. The placenta was retained until the one hundred and fifty-first day of gestation, and both ureters returned to normal on the fourth day afterward.

Van Wagenen and Jenkins concluded that dilatation of the upper portion of the urinary tract can develop after removal of the fetus and while the placenta remains in a functional state within the uterus. It would appear, therefore, that this physiologic change is related primarily to the stage of pregnancy and secondarily to the influence of the increased weight of the uterus with its contents in pregnancy.

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30. van Wagenen, G., and Jenkins, R. H.: An Experimental Examination of Factors Causing Ureteral Dilatation of Pregnancy, J. Urol. **42**:1010-1020 (Dec.) 1939.

Injury.—Östling [31] described a case in which a ureter which during a pelvic operation had chanced to be severed 9 cm. above the bladder was immediately sutured over a catheter brought out through the urethra. Eight and a half years later excretory urographic examination showed a normal renal pelvis on the damaged side. A constriction was revealed at the seat of the suture, and immediately above this the ureter was found to be slightly dilated. This constriction corresponded to a valvular formation, preventing catheterization and retrograde pyelographic procedures. Since the view held concerning the prognosis of ureteral suture is based on experiences encountered before urography came into use, according to which treatment in a case like that of Östling would have been counted as a failure, and since the literature affords no binding proofs that the results are particularly bad, it does not seem unlikely that after-examination by urographic methods might bring about a reassessment of the functional capacity resulting from ureteral suture after transverse section.

Rusche and Bacon [32] stated that ureteral trauma occurs most commonly in the course of surgical procedures on the internal genitalia of the female, next as a result of cystoscopic intraureteral instrumentation or of external violence and finally as the result of the presence of foreign bodies.

The present increase in the incidence of ureteral injury is referable mainly to recognition of the pathologic lesion. Unquestionably the actual incidence is not known, because unilateral ligation of the ureter results in numerous instances in unrecognized destruction of the kidney.

Rusche and Bacon unqualifiedly recommended ureteral catheterization as the method of prevention of ureteral injury in surgical conditions that are considered preoperatively to be difficult.

The treatment of an injured ureter should consist of initiation of the procedures that will preserve, ultimately, the function of the ureter and kidney. Treatment is dependent on the time of recognition of the injury, the type and situation of the injury and the condition of the patient.

If complete ureteral division is discovered at the time of operation, ureterovesical implantation or ureteroureteral anastomosis is the procedure of choice if the operation will not be hazardous.

When a segment has been removed, ureterointestinal or ureterocutaneous anastomosis or ligation is recommended.

Bilateral ureteral occlusion, recognized postoperatively, requires bilateral nephrostomy. The procedure of deligation is to be condemned.

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31. Östling, K.: Zur Kenntnis der Spätresultate bei Naht des querdurchtrennten Harnleiters, Acta chir. Scandinav. **83**:74-82, 1939.

32. Rusche, C. F., and Bacon, S. K.: Injury of the Ureter Due to Surgery, Intra-Ureteral Instrumentation, External Violence and Foreign Bodies: Report of Fifty Cases, J. A. M. A. **114**:201-207 (Jan. 20) 1940.

Intraureteral instrumentation as a cause of ureteral injury is dependent usually on impaction of a calculus and adjacent disease of the ureter. The present increase in the incidence of ureteral perforation is related closely to the recent development of many devices designed to remove calculi.

PROSTATE GLAND

Hypertrophy.—Abeshouse,[33] after a study of 200 consecutive transurethral resections and 234 prostatectomies, concluded that transurethral resection deserves a definite place in the operative treatment of prostatic obstruction. It is the operation of choice in cases of median bar, solitary median lobe and solitary subcervical hypertrophy. Excellent results also may be obtained in instances of small or moderate-sized enlargement of the median or lateral lobes. The operation affords palliative relief in cases of carcinoma in which there are obstructive symptoms; it provides an excellent method of removing obstruction caused by contractions, nodules or tags following prostatectomy, and it is valuable in cases of persistent suprapubic fistula. Abeshouse stated the belief that the operation is not suitable in cases in which "large bilobed or trilobed hypertrophy" with marked intravesical or intraurethral bulging is present.

Suprapubic prostatectomy is suitable for cases in which marked enlargement of the prostate gland is present, especially if this is accompanied with vesical conditions requiring operative treatment. The operation requires no unusual operative skill and insures a good and permanent functional result.

Perineal prostatectomy is an ideal operation for the treatment of large hypertrophy and small fibrotic glands with or without prostatic calculi. It is the only method offering a cure of early or concealed carcinoma. It requires greater operative skill and, when properly done, insures an equally good functional result. The fear of incontinence, impotence and fecal fistula is dispelled by complete mastery of the operative technic.

LeDuc [34] described a method by means of which the internal structure and distribution of the prostatic duct systems may be studied visually.

Anatomically, the prostate gland may be considered to be composed of two major lobes (the lateral lobes) and of a smaller, median lobe; the latter may sometimes be replaced by a prespermatic commissure consisting of interlacing lateral lobe ducts.

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33. Abeshouse, B. S.: A Comparison of Results in the Treatment of Prostatic Obstruction by Transurethral Resection and Prostatectomy, J. Urol. **42**:1101-1122 (Dec.) 1939.

34. LeDuc, I. E.: The Anatomy of the Prostate and the Pathology of Early Benign Hypertrophy, J. Urol. **42**:1217-1241 (Dec.) 1939.

The situation of the orifices of the ducts may be correlated fairly accurately with the portion of glandular tissue drained by them. 1. Those on the lateral urethral walls, in the prostatic sulci and on the verumontanum and inferior crista drain corresponding portions of the lateral lobes, laterally or obliquely-laterally, to the orifice of the duct. 2. Those on the superior crista drain the median lobe or the tissue in the mediolateral commissure.

Microscopic studies of the earliest lesions of benign hypertrophy offer confirmatory evidence in support of the theory promulgated by Reischauer and confirmed by Deming and Neumann that the essential lesion of prostatic hypertrophy is the nodular proliferation of fibrous tissue, in which glandular penetration and growth take place only as secondary phenomena.

The glands taking part in the formation of prostatic hypertrophy appeared in this study to be entirely of the submucosal type.

Smith [35] stated that prostatic obstruction may be caused by cancer, fibrosis or hyperplasia.

Hyperplasia is believed by some authorities to develop only in the submucous glands of the urethra. Others believe that it may also develop in the lateral lobes themselves.

Experimental evidence seems to prove that in certain animals hypertrophy of the prostate gland is caused by deficient secretion of inhibin, a hormone secreted by the tubular epithelium of the testicle. Doubt exists as to whether the type of hypertrophy so produced is analogous to the prostatic hyperplasia found in man, but the fact that hypertrophy develops only as the sexual function begins to wane makes it seem likely that this theory is the most probable of all that have been suggested.

After therapy based on this hypothesis, definite improvement has been noticed in a majority of patients. Equally good results have been claimed by a few urologists who have treated patients suffering from hypertrophy of the prostate gland by roentgen or radium therapy and also have been observed in a series of 93 patients who were not treated by operation, by irradiation or by glandular therapy.

Smith reviewed the various methods of operative removal of the obstructing prostatic tissue. In his opinion, transurethral resection is the best method for prostate glands which are not readily enucleable, as is true in the majority of instances of prostatic cancer, small, fibrous prostate glands and small hypertrophy. These cases constituted 41 per cent of a series of prostatic operations done in the last six years. For larger hypertrophy, open operation is preferable. Prostatectomy is not an obsolete operation.

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35. Smith, G. G.: The Obstructing Prostate: Its Treatment, Surgical and Otherwise, J. Urol. **42**:145-157 (Aug.) 1939.

Cancer.—Wishard, Hamer and Mertz [36] presented a series of 224 cases of carcinoma of the prostate gland. Of these, the patients in 148 were treated surgically (120 by resection), and 76 were treated nonoperatively. The average age was 65 to 70 years. The majority of the patients were hospitalized two to four weeks for prostatic resection.

Thirty-four per cent of the patients in the series could not be operated on, chiefly because of metastases to bones, symptoms too mild to necessitate operation, severe renal lesions and death which occurred before anything could be done. Two thirds of the patients not treated surgically died within the first year after the diagnosis had been established.

Patients sought relief primarily because of dysuria, vesical irritability and retention of urine. Almost half of the patients receiving surgical treatment had complete retention of urine before operation; about 75 per cent had less than 1 fluid ounce (30 cc.) of residual urine at the time of dismissal from the hospital.

The amount of tissue removed at resection in the majority of instances was less than that removed by resection for benign hypertrophy of the prostate gland. Multiple resections were required for about a fourth of the patients.

Rectal and cystoscopic examination disclosed grade 2 enlargement as the customary observation. A soft prostate gland was found by rectum in almost 10 per cent of the cases. Pathologic examination revealed that the condition of more than 10 per cent of the glands would have been erroneously considered benign if reliance had been placed entirely on clinical observations.

Roentgen examination revealed osseous metastases in 31 per cent of the patients examined. The fourth lumbar vertebra was the point of predilection.

In Wishard, Hamer and Mertz's experience the operative risk of resection has not been negligible. Seven per cent of the private patients and 15 per cent of the ward patients died after resection and before leaving the hospital. Death was referable almost exclusively to cardiac, pulmonary or renal causes. The total "hospital death rate" for all patients, both those who underwent operation and those who did not, was 13 per cent for the private patients and 29 per cent for the ward patients. Forty per cent of the patients who underwent resection and who left the hospital alive were known to be dead within two years after their departure therefrom.

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36. Wishard, W. N., Jr.; Hamer, H. G., and Mertz, H. O.: Transurethral Resection in Treatment of Carcinoma of Prostate, J. Urol. **42**:1088-1100 (Dec.) 1939.

Abscess.—Hammer and Thompson [37] reported a case of chronic prostatic abscess with these three considerations in mind: (1) Chronic prostatic abscess is a comparatively rare complication of chronic prostatitis; (2) diagnosis may be difficult and may require intensive urethroscopic examination, and (3) the condition may be satisfactorily treated by transurethral operation. The patient was a man 31 years of age who presented a history of backache of increasing severity and perineal discomfort when sitting, so that he had been unable to work as a truck driver. He also had lassitude and recurring bouts of fever. Treatment elsewhere with urinary antiseptic agents had failed to clear pyuria and bacilluria (Pseudomonas) because of the presence of prostatitis grade 4. Administration of mandelic acid and local treatment, followed by tonsillectomy and administration of sulfanilamide, also failed. Urethroscopic examination revealed purulent material to be exuding from the dilated prostatic ducts and also from the ejaculatory ducts. The cavity of an abscess 3 cm. in diameter was unroofed by the resectoscope, and the walls of this cavity were excised. The patient left the hospital in two days and voided clear urine five days later for the first time. The backache and perineal discomfort disappeared at the same time. Prostatic massage is contraindicated postoperatively. Surgical treatment is contraindicated in the ordinary case of diffuse chronic prostatitis.

Prostatic Fluid.—Experimental studies by Barnes [38] have shown that human prostatic fluid contains a substance which has a definite pharmacologic action and which when administered in comparatively large doses is toxic. This substance was shown to exert a marked toxic effect when given to rats in doses of 1 cc. intraperitoneally, and sometimes this dose reduced the activity of the animals almost to nil. No tolerance to this substance is developed by giving repeated increasingly large doses to rats, and small doses repeated daily have little, if any, cumulative effect. The most marked and constant pharmacologic action of this substance was found to be, experimentally, depression of blood pressure and marked stimulation of smooth muscle in vitro.

This experimental investigation shows that normal human prostatic fluid as obtained by prostatic massage has a definite, constant and marked pharmacologic action which is not identical with that of any other substance now known. Because of this definite action, prostatic fluid must have a function other than that which has been ascribed to it; that is, neutralization of the acid vaginal secretions, producing a more suitable medium for the life of spermatozoa. The action on smooth

37. Hammer, H. J., and Thompson, G. J.: Chronic Prostatic Abscess: Report of Case, Proc. Staff Meet., Mayo Clin. **14**:446-447 (July 12) 1939.

38. Barnes, R. W.: An Experimental Study of the Pharmacology of Prostatic Fluid, J. Urol. **42**:1207-1216 (Dec.) 1939.

muscle would suggest that the substance has the function, after it is absorbed through the vaginal mucosa, of producing antiperistalsis in the uterus to aid in the dissemination of spermatozoa.

BLADDER

Tumor.—Vermooten [39] reported a case of rhabdomyomyxosarcoma of the bladder. Such cases are very rare.

The patient was a girl aged 20 months. Because of retention of urine she was catheterized twice daily until five days later, when a portion of the tumor prolapsed into the urethra. The child was given a general anesthetic, presumably to reduce the prolapse, and died under anesthesia. At necropsy extensive bronchopneumonia was observed in both lungs. There were multiple abscesses in both kidneys. Associated with the pyelonephritis was mild bilateral hydronephrosis, with dilated, tortuous and infected ureters. The bladder contained a tumor which arose from a pedicle 1 cm. long and 0.5 cm. wide, overlying the trigon. It had the appearance of a large bunch of grapes and consisted of two main masses. The mass immediately connected to the pedicle had a diameter of about 7 cm. and was 4 cm. long. Attached to this mass by a very narrow pedicle was the main tumor mass, measuring 8 cm. in length and at its widest point having a diameter of 5 cm. In addition to the main tumor mass there were two other portions adjacent to the pedicle, in which apparently new tumors of the same type were beginning to form.

The microscopic picture as described by the pathologist of the South African Institute for Medical Research "revealed that the lobules of the tumor were made up of cellular and myxomatous areas enclosed in coverings of transitional epithelium of normal type. In the cellular areas and scattered throughout the myxomatous tissue elongated fibres of striped muscle and large rounded acidophilic cells exhibiting a fibrillar cytoplasm and radial striation were seen."

Orr, Carson and Novak [40] presented a study of clinical results obtained in the treatment of malignant tumors of the bladder by 267 surgeons. An analysis of more than 26,000 cases of vesical carcinoma forms a basis for this discussion. This analysis was obtained through the medium of a questionnaire in an effort to ascertain the method of treatment which would give the patient the greatest degree of comfort and the longest life.

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39. Vermooten, V.: Rhabdomyomyxosarcoma of the Bladder: Case Report, J. Urol. **42**:126-130 (Aug.) 1939.

40. Orr, L. M.; Carson, R. B., and Novak, W. F.: A Statistical Study of Present-Day Methods Used in the Treatment of Tumors of the Bladder, J. Urol. **42**:778-788 (Nov.) 1939.

For the sake of convenience, the questionnaire was divided into two sections, one, "Conservative Treatment," including all methods of treatment other than total cystectomy, and the other, "Radical Treatment," including only total cystectomy and ureteral transplantation. Of the two hundred and sixty-seven surgeons reporting, two hundred and twenty-one favored conservative methods of treatment, and only eight favored radical treatment, or total cystectomy. The conservative methods used have been set forth in detail.

Of all methods used in the treatment of tumors of the bladder, fifty-one surgeons considered segmental resection of the bladder to be the one which would afford the patient the most comfort and the longest life.

Three hundred and fifty-three cases of total cystectomy and ureteral transplantation have been collected. An average mortality rate of 33.2 per cent attended the operation. Ninety-two patients died during the first year. Eighteen patients had lived more than five years at the time Orr, Carson and Novak wrote, although the majority of the operations had been performed during the five years prior to the time of writing.

The reasons for not performing total cystectomy as given by fifty-seven surgeons were that the operation is too radical and the mortality rate too high. Sixty-six stated that the patients when seen were too old, the disease was too far advanced, or renal damage had already occurred; nine cited difficulties in convincing patients and the referring physician; fourteen stated that cystectomy should be performed more often in suitable cases, and twelve admitted that they did not have enough surgical experience.

This study has definitely brought out again the necessity for early diagnosis in instances of cancer of the bladder. Education not only of the laity but of the general practitioner should be continued according to methods which will result in earlier examination by the urologist of patients who have symptoms of tumor of the bladder.

Metastasis to regional lymph nodes and distant organs is probably more rapid than has heretofore been assumed.

Lowrey [41] reported 5 cases of adenocarcinoma of the bladder; 3 of the 5 lesions were situated in the dome, and the remaining 2 in the base, of the bladder. These tumors showed three gradations of malignancy. One tumor was relatively benign, and both adenoma and adenocarcinoma were found in the same growth. Two tumors showed a moderate degree of malignancy; the patient had been comparatively well during a three year period. Two other tumors were of the rapidly growing type, and secondary growths were found to involve the regional and iliac lymph glands a short time after the onset of symptoms.

41. Lowrey, S. R.: Adenocarcinoma of the Bladder, J. Urol. **42**:118-125 (Aug.) 1939.

Shivers and Henderson,[42] in a discussion of a group of 101 cases of tumor of the bladder, stated that 19 of 32 patients presenting tumors with narrow attachments to the wall of the bladder are living, and that none, so far as the authors know, have died of the disease. The longest interval has been fourteen years. Five died from other causes, and the authors were unable to communicate with 8. All of the patients were treated by surgical diathermy, either transurethrally or transvesically.

In a group in which the tumors showed a wide attachment to the wall of the bladder, there were 35 cases. Fifteen patients were dead as a result of the disease; 4 died from other causes, and contact could not be made with 9. Only 7 in this group heard from were still living at the time of writing. One patient had survived for seven years, with a bladder apparently normal on examination.

In the group of 34 cases of infiltrating carcinoma, all but 2 of the patients are now dead. These patients received high voltage roentgen and radium treatment with or without surgical treatment. The 2 surviving patients had lived, at the time Shivers and Henderson wrote, eight years after the transvesical implantation of radon.

The importance of careful follow-up treatment cannot be overemphasized. It is Shivers' and Henderson's custom, they stated, to use cystoscopic methods for these patients at monthly intervals for the first year and as often thereafter as they deem it necessary.

Transurethral resection has a very important place in the treatment of vesical tumors of the pedunculated type if they are suitably situated.

Shivers and Henderson have not resorted to any radical surgical procedure in the treatment of tumors of the bladder, because most of their patients who presented extensive involvement of the wall of the bladder were poor risks. They stated the belief that when cancer of the bladder has developed to a point at which less radical means of treatment cannot be used, the possibility of performing cystectomy has usually passed because of the poor physical condition of the patient, which is the result of urinary sepsis, secondary anemia or renal insufficiency. The authors stated that they feel justified under such conditions in choosing a procedure which will prolong the patient's life in as much comfort as possible, rather than in attempting a cure.

Kickham and Jaffe,[43] in discussing the upper portion of the urinary tract in the presence of tumors of the bladder, stated that there is a marked tendency of vesical growths to be situated in proximity to the ureteral orifices. They emphasized the high incidence of pathologic

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42. Shivers, C. H. de T., and Henderson, K. P.: Tumors of the Bladder: A Review of One Hundred and One Cases, J. Urol. **42**:761-777 (Nov.) 1939.

43. Kickham, C. J. E., and Jaffe, H. L.: The Upper Urinary Tract in Bladder Tumors, J. Urol. **42**:131-139 (Aug.) 1939.

changes, obstructive and septic, in the upper portion of the urinary tracts of patients with malignant disease of the bladder.

They stated the belief that it is of paramount importance to determine the status of the upper portion of the urinary tract prior to the institution of treatment (so that patients who have ureteral occlusion may be properly managed). Measures for prophylaxis are recommended in the absence of ureteral obstruction to insure adequate renal drainage in the event that acute or delayed obstructive changes occur.

The end results in the management of tumors of the bladder will be materially improved if death from renal insufficiency is prevented. The proper drainage of obstructed kidneys may secure relief from distressing symptoms and prolong the life of those patients in whom the status of the disease in the bladder offers a hopeless prognosis.

Diverticulum.—Thompson, Kermott and Cabot [44] stated that diverticulum of the urinary bladder is of congenital origin and that it generally causes no symptoms until obstruction develops at the vesical outlet; the obstruction usually is caused by benign prostatic hyperplasia but may be the result of contracture of the vesical neck, congenital obstruction or prostatic carcinoma.

If the obstruction at the vesical outlet is to be removed by suprapubic operation, it is best to precede this operation by diverticulectomy, performed generally as a first stage procedure.

In the large majority of instances thorough transurethral resection of the tissue obstructing the vesical neck will relieve the patient's symptoms, and diverticulectomy will not be required. If the symptoms are not satisfactorily relieved, diverticulectomy can be performed subsequent to transurethral prostatic resection; the latter operation in no way adds to the technical difficulty of removing the diverticulum.

An analysis of the results obtained in 96 patients who were treated only by transurethral resection of the obstruction at the vesical neck warrants the conclusion that in patients of the age group likely to have prostatic disorders the risk, discomfort and prolonged hospitalization incidental to diverticulectomy can almost always be avoided.

Cystitis Cystica.—Craig [45] stated that cystitis cystica glandularis is a response of the mucous membrane of the bladder to chronic irritation. The evidence does not indicate that the glands are necessarily the result of embryonal misplacement of intestinal epithelium. The condition probably develops by means of a process of metaplasia of the epithelium,

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44. Thompson, G. J.; Kermott, L. H., and Cabot, H.: The Management of Diverticulum of the Bladder: Ninety-Six Patients Treated by Transurethral Prostatic Resection, Surg., Gynec. & Obst. **70**:115-119 (Jan.) 1940.

45. Craig, L. G.: Cystitis Cystica Glandularis, J. Urol. **42**:1197-1203 (Dec.) 1939.

passing through the stages of the cell nests of Brunn, cystitis cystica and, later, cystitis glandularis. The formation of glands appears to involve an active secretory process in the cells rather than a mere degeneration of the central cells of the Brunn's nests. Cystitis cystica glandularis is potentially, but not actually, malignant and may be the point of origin of adenocarcinoma of the bladder.

Tabetic Changes.—Emmett [46] stated that disturbance of vesical function constitutes one of the most aggravating symptoms of tabetic cord bladder. It usually is described in textbooks on neurology as "difficulty in urination, urinary retention and incontinence." As a matter of fact, true incontinence in the presence of tabes dorsalis is not common. In most instances so-called incontinence, if carefully studied, will be found to result from overflow from a distended bladder or from urgency referable to infection of the urinary tract which has been initiated by the retention of urine.

The diagnosis of cord bladder usually has been based on the cystoscopic observations which follow: reduction in expulsive force of the bladder, trabeculation, relaxation of the vesical neck (the internal vesical sphincter) and diminution in sensation. In a large number of cases the atonicity and trabeculation of the bladder were the only observations apparent. In reality, therefore, the diagnosis of tabetic cord bladder in such cases simply indicated the presence of an atonic bladder with retention of urine, occurring in the presence of tabes dorsalis. That the tabetic condition was responsible for the vesical disturbance was only surmised. When such a system of diagnosis was employed, retention of urine in many cases was diagnosed as "cord bladder," whereas, if the truth were known, the condition was entirely unrelated to the neurologic disease.

Newer concepts of the physiologic aspects of micturition suggest that the act of micturition results from the contractile response to stretch of muscle fibers of the bladder.

In recent years transurethral resection has been performed at the Mayo Clinic for a group of patients with such symptoms, with exceptionally good results. The former fear of postoperative incontinence is no longer present, since it is known now that if no true incontinence exists before operative intervention there will be none afterward if the external sphincter (compressor urethrae muscle) has not been injured. Resection of the vesical neck in a case in which the obstruction is extremely minimal (such as a very slight contracture) will often restore perfect vesical function even in cases in which a large amount of residual urine has been present. Also, the observation is made that many con-

46. Emmett, J. L.: "Tabetic Cord Bladder": Newer Concepts in Diagnosis and Treatment, Proc. Staff Meet., Mayo Clin. **15**:91-96 (Feb. 7) 1940.

ditions which formerly were diagnosed as "tabetic cord bladder" are in reality simple obstruction of the vesical neck in which the associated tabes dorsalis plays little, if any, part. Combinations of various degrees of obstruction of the vesical neck and neurologic involvement make diagnosis interesting.

Emmett reported several cases, in 1 of which a man aged 63 years underwent neurologic examination, which revealed observations typical of tabes dorsalis. There was retention of 1,500 cc. of urine. Eight grams of tissue was removed by transurethral resection, after which the patient was able to empty his bladder completely. This was an instance of true tabetic cord bladder associated with mild obstruction of the vesical neck.

Malakoplakia.—Rudnick and Ragins [47] reported a case in which a white woman 53 years old had malakoplakia associated with chronic ascending unilateral pyelonephritis, nephrolithiasis and chronic ureteritis. The plaques were composed of large polygonal cells containing Michaelis-Gutmann bodies and also large accumulations of lymphocytes and plasma cells. The cells were entirely distinct from those of the transitional epithelium covering them, as was shown by various differential stains.

Bacteriologic studies revealed the chief organism to be Bacillus mucosus capsulatus (Friedländer's bacillus), which was isolated from the urinary bladder and from the left ureter.

On removal of the left kidney and ureter all the symptoms and the malakoplakia disappeared.

Drainage of Prevesical Space.—Chute [48] discussed drainage of the prevesical space. Because of the fascia which covers the muscles that form the urogenital pelvic diaphragm there is no way in which the prevesical space can drain itself. Infection tends to remain and to spread because of the loose, fatty tissue. Consequently, if the space is not drained or if the drain is removed too early a poorly drained septic pocket is left, resulting in a slowly healing wound or in formation of an abscess. In Chute's opinion, extensive suppuration in this space accounts for some of the instances of pericystic infection, periostitis or even osteomyelitis of the pubic bone. He cited 2 cases in which complications resulted from premature withdrawal of the drain. He stated that withdrawal of the drain should not be started until six days have elapsed and until the temperature has returned to normal and that the drain should then be shortened daily.

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47. Rudnick, D. F., and Ragins, A. B.: Malakoplakia of the Bladder, J. Urol. **42**:108-117 (Aug.) 1939.

48. Chute, R.: A Note on Drainage of the Prevesical Space, New England J. Med. **220**:108-109 (Jan. 19) 1939.

Rupture of Inflammatory Masses into Bladder.—Falk and Hochman [49] stated that spontaneous rupture of pyosalpinx or pelvic abscess into the bladder occurs.

The symptoms and signs are usually masked by the underlying pathologic process. Rupture of a pelvic inflammatory mass into the bladder is usually shown by the sudden appearance or marked increase of pus in the urine, with severe "urinary symptoms," such as frequency of urination, burning and tenesmus. Such symptoms are very significant if they are followed by improvement in the patient's condition and recession of temperature.

Cystoscopic study establishes the diagnosis, revealing an area of bullous edema from the center of which pus exudes.

The fistula usually heals spontaneously, recession of the mass being achieved by medical treatment or by surgical intervention.

Patients who come for gynecologic treatment with a pelvic mass should have routine investigation of the genitourinary tract, including cystoscopic study, because the presence of local edema of the vesical mucosa from a contiguous inflammatory mass may be a premonitory sign of perforation.

Three cases of rupture of a pelvic infection into the urinary bladder, with a collection of 21 cases from the literature, are reported.

URETHRA

Infection.—In a series of 40 cases of sulfanilamide-resistant gonorrhea reported by Alyea and Daniel,[50] 55 per cent of the patients were cured with sulfanilylsulfanilamide. Sulfanilylsulfanilamide probably has a greater specificity for certain strains of gonococci. Smaller daily doses than were formerly advocated are effective. The interrupted method of administration is recommended. To wait for therapeutic maturity is not recommended as a routine procedure. Clinically, sulfanilylsulfanilamide is more easily tolerated than is sulfanilamide. Peripheral neuritis was the only serious toxic reaction encountered, and it occurred once in this series of 40 cases.

Johnson, Leberman, Pepper and Lynch [51] noted the results of a follow-up study in which 63 of 80 male patients suffering from gonorrheal urethritis were treated with sulfapyridine. Of these 63 patients, 50 (79.2 per cent) passed all the tests of cure, the average duration of

49. Falk, H. C., and Hochman, S.: Rupture of Pelvic Inflammatory Masses into the Urinary Bladder, Am. J. Obst. & Gynec. **38**:654-651 (Oct.) 1939.

50. Alyea, E. P., and Daniel, W. E.: Treatment of Sulfanilamide-Resistant Gonorrhea with Sodium Sulfanilyl-Sulfanilamide, J. Urol. **42**:864-873 (Nov.) 1939.

51. Johnson, S. H.; Leberman, P. R.; Pepper, D. S., and Lynch, H.: Use of Sulfapyridine in the Treatment of Gonococcal Urethritis in the Male, Am. J. M. Sc. **198**:594-602 (Nov.) 1939.

discharge in these cases being two and seventy-seven hundredths days. The dose was 3 Gm. of sulfapyridine a day for four days, followed by 2 Gm. a day for six to ten days. In a group of 19 patients whose condition had been resistant to previous treatment with a sulfanilamide derivative, 68.4 per cent were cured with sulfapyridine administered thereafter. Forty-five patients (56.2 per cent) had one or more toxic reactions. Values for sulfapyridine in the blood were of no significance in prophesying reactions or cures. In the authors' experience, sulfapyridine has been the most efficient sulfanilamide derivative in the treatment of gonococcic urethritis in the male.

Abscess.—Schmitz and Nelson [52] reported 8 cases of suburethral abscesses, urine pockets and diverticula in the female urethra. More than 100 cases of diverticulum of the female urethra have been reported. Many names are applied to the disorder—"urethrocele," "cyst," "abscess," "urinary pocket" or "urinary pouch." However, the three previously mentioned conditions should not be confused with abscesses or cysts of Skene's glands, vaginal cysts or small vaginal myomas. Urethral diverticula may be classified as either true or false. When all the layers of the urethra are involved in the process, they are called "true diverticula." False diverticula are those in which only the submucosa and mucosa protrude, the muscularis having ruptured.

The symptoms produced by urethral diverticula are directly referable to the genitourinary tract. Pain, frequency of urination and burning are nearly always present in this condition, but involuntary loss of urine is the most annoying symptom and is rather constant. Passage of bloody urine is an associated symptom in a few cases. Swelling noticeable to the patient is an infrequent symptom. The diagnosis of urethral diverticula is based on careful examination of the urethra and vagina. A history of urinary difficulty associated with involuntary soiling, together with the discovery of a collapsible bulge in the vagina over the urethra, leads to the suspicion of diverticulum. If urine can be expressed from the mass into the urethra after the bladder has been emptied by voiding or catheterization, the diagnosis is made even without visual intraurethral examination. The diagnosis is absolute after direct visualization of the diverticulum opening on urethroscopic examination. The pocket also may be filled with opaque material and then examined by roentgen rays. Skene's abscesses are excluded by reason of their situation. Solid tumors or cysts do not collapse under pressure.

The treatment of choice for this deformity is surgical removal of the diverticulum. Electrocoagulation of the duct and sac is not advised. Suprapubic drainage is uncalled for except in instances of complication.

52. Schmitz, H. E., and Nelson, P. A.: Suburethral Abscesses, Urine Pockets and Diverticula in the Female Urethra, Am. J. Obst. & Gynec. **38**:707-711 (Oct.) 1939.

Resistance.—Langworthy, Drew and Vest [53] stated that the collapsed urethra offers a certain resistance to the escape of urine from the bladder. In addition, they recognized three more specialized sphincteric mechanisms which can be distinguished in the experimental animal. The vesical orifice is normally closed and is pulled open by the contraction of the detrusor muscle and by the increased intravesical pressure. Sympathetic nerve fibers innervate muscle in the region of the verumontanum; this muscle has a sexual function and is particularly well developed in the male. Finally, the external sphincter and the perineal muscles form a voluntary sphincter. Section of the pudendal nerves, the sacral nerve roots and the sympathetic nerve fibers did not alter materially the urethral resistance. Abnormalities of micturition referable to injury of the nervous system are dependent primarily on difficulties of contraction of the detrusor muscle and only secondarily on changes in urethral resistance. The term "sphincter disturbances" is a misnomer.

TESTICLE

Tumors.—Shane [54] reported a case of tumor of the testis in an infant. The child was 4 months old. Two weeks after birth of the child the mother first noticed an enlargement of the left testicle. Both testicles were descended; the right testicle was normal in size, but the left had enlarged to the size of a small hen's egg. The testicle was removed at operation, and on examination the tumor was found to be well circumscribed and not extended beyond the limiting capsule. Microscopic examination showed the tissue to be primary embryonal carcinoma, grade 2. Five months later the patient was in good health, with no evidence of recurrence.

Cabot and Berkson [55] gave survival rates concerning 73 patients treated at the Mayo Clinic for testicular tumor and known massive metastasis. Forty-seven patients received irradiation alone; 26 underwent orchidectomy followed by irradiation (13 had carcinoma; 13 had seminoma). Of the 47 patients, a group for whom the outlook appeared particularly unfavorable, only 17 per cent survived at the end of three years, and only 11.6 per cent were living at five years. Some patients lived as long as nine, thirteen and sixteen years. Of the cases in which orchidectomy was followed by irradiation, with known massive metastases, 38.5 per cent of the patients were alive at the end of three years;

53. Langworthy, O. R.; Drew, J. E., and Vest, S. A.: Urethral Resistance in Relation to Vesical Activity, J. Urol. **43**:123-141 (Jan.) 1940.

54. Shane, J. H.: Tumor of the Testis in an Infant, J. Urol. **42**:236-239 (Aug.) 1939.

55. Cabot, H., and Berkson, J.: The Outlook for Patients with Malignant Tumors of the Testis Associated with Massive Metastasis, Proc. Staff Meet., Mayo Clin. **14**:377-380 (June 14) 1939.

32 per cent were alive at the end of five years, and 26.7 per cent were alive at the end of ten years. Of these, for the patients who had carcinoma the five year survival rate was only 15.4 per cent; for those who had seminoma it was 50 per cent. Analyses of all cases in which the patients survived three years or more are given in two tables.

Chevassu and Carrillon [56] drew attention to cancers of the testicle which developed on testicles that had been ectopic and that had been brought down surgically. Chevassu has had only 2 patients suffering from this condition among 350 patients who had tumors of the testicle and who came to consult him; Carrillon contributed reports on 3 more, from the urologic service at the Val-de-Grâce hospital. In Carrillon's cases the histologic diagnoses were: epithelioma developing from wolffian rests; neoplasm of the wolffian type suggesting a cancerous dysembryoma, and dysembryoma of the wolffian type in a state of degeneration. Chevassu took some exception to a diagnosis of wolffian epithelioma, writing that he has not seen any cancers of the testicle that could be ascribed frankly to this origin.

In Chevassu's first case, in which the patient was a man aged 42, the lesion was proved histologically to be a seminoma. The cancerous testicle had been brought down from its ectopic position sixteen years previously and had remained in good condition until one year prior to Chevassu's observation. Operation and roentgen therapy reduced the tumor from the size of a fist to that of a bean, after which it refused to shrink further. A second series of treatments had no effect. The cancer metastasized, and the patient is known to have died in the following year. This experience caused Chevassu to protest against simple radiation therapy. In his second case he treated the patient by surgical removal of the lesion followed by two series of roentgen treatment and has achieved a three year cure, with this patient in excellent condition at the time of writing.

In the French literature there are only 14 cases on record of ectopic testicle in which cancer developed. These were the cases of Chauvin, Fey and the present authors. Five of the testicles were brought down in childhood, when the patients were 8, 9, 11, 13 and 13 years old respectively. The cancers that developed were treated surgically when the patients were respectively 30, 36, 20 and 23 years old. In other words, the interval was long—between seven and twenty-three years. In 7 cases the testicle was brought down when the patients were 15, 20, 20, 26, 26, 27 and 32 years old, and the carcinoma was removed when the patients were 15, 25, 35, 26, 42, 43 and 33 years old respectively.

56. Chevassu, M., and Carrillon, R.: Cancers testiculaires développés sur les testicules ectopiques après leur abaissement opératoire, J. d'urol. **47**:59-70 (Jan.) 1939.

Thus, in 3 of these cases the interval was very short, but in 3 it was sixteen years.

It is evident that 14 cases represent an exceedingly small fraction of the cases of ectopic testicles that have been brought down into the scrotum. The question then arises: Must one conclude that testicles brought down are less likely to become afflicted by cancer than those that are left undescended? The frequency of carcinomatous degeneration of ectopic testicles must not be exaggerated. In Chevassu's series of 350 cases of cancer of the testicle, the number of ectopic testicles is only a few units. If such testes are predisposed to cancer, there is no proof of it, and such a predisposition does not appear to exist.

Chevassu expressed the tentative opinion that trauma facilitates the development of cancer of the testes. What role does ectopia play in trauma? Does orchidopexy represent a trauma? The 3 cases of Chauvin in which this operation was followed by carcinoma a few months later suggest that operation for ectopia may be more dangerous than ectopia itself.

It is difficult to know what advice to give in cases of ectopia. Possibly the urologist has the right to urge on the parents of children realization of the frequency with which an ectopic testis may become cancerous, but it seems doubtful that he has the right to urge on adults the sacrifice of a testicle on the ground that it may have a predisposition to cancer. The medical literature contains only 6 cases in which ectopic testicles brought down in adults became malignant. It seems probable that the urologist should explain to the patient (or to the parent, if the patient is a child), that this testicle is, at any rate, fragile and that it needs watching. After it has been brought down the patient should be kept under observation and examined from time to time to see if any change is occurring in the organ. Too many instances of cancer of the testicle are encountered by the surgeon too late because the patients have not been warned of the dangers of changes in size or consistency of the organ. The patient whose ectopic testicle has been operated on especially should be under observation. It must be said, however, that the number of cases in which cancer has developed in such testicles is at present too small for any valid conclusion to be reached.

Hunt and Budd [57] reported an instance of gynecomastia associated with interstitial cell tumor of the testicle. The patient was a man aged 42. He complained of enlarged, painful breasts and impotence. Both breasts were approximately equally hypertrophied, and a definite mass of mammary tissue could be outlined in each. The breasts were tender to pressure, but no tumor or nodule was palpable. The testicles

57. Hunt, V. C., and Budd, J. W.: Gynecomastia Associated with Interstitial Cell Tumor of the Testicle, J. Urol. **42**:1242-1250 (Dec.) 1939.

were of approximately the same size and were uniform in outline, but there was a slight difference in their consistency. On careful palpation of the right testicle a slight difference in the consistency between the upper and the lower pole was noticed, suggesting the existence of a tumor of about 2 cm. in diameter within the substance of the upper pole of the testicle.

A positive reaction to the Zondek test equivalent to "1,000 units of luteinizing hormone per liter of urine" was obtained by Dr. Mona E. Bettin. A diagnosis of tumor of the right testicle was made, and surgical exploration of the testicle was advised.

Through a right inguinal incision the right testicle was found to be normal in size and contour, but the slight difference in consistency between the upper and the lower pole was sufficiently definite to warrant incision of the testicle for confirmation. Immediately after exposure of the tumor, the testicle was removed, together with all the structures of the cord as high as the level of the internal inguinal ring.

The patient had an uneventful convalescence and was dismissed from the hospital on the fifth postoperative day. There was return of libido immediately after the operation, and within a month there was a definite reduction in the size of the breasts, somewhat less in the right breast than in the left. The patient was seen at frequent intervals, and three months later the left breast had receded almost to its normal size, some prominence of the right breast persisting.

The testis was of normal contour and average size, measuring 5 by 3.5 by 3 cm. An incision in the upper pole had exposed an encapsulated tumor 2 by 2 by 2.5 cm., deep in the testicular substance. As the tumor was enucleated from the testicle, it appeared to be attached to the upper part of the corpus of Highmore by a fibrous pedicle. The surrounding testicular parenchyma was compressed and pale yellow. No change was noted in the cord or in the epididymis. The capsule of the tumor was a smooth, thin, transparent membrane containing numerous dilated blood vessels.

The diagnosis was interstitial cell tumor of the testis.

Orchiopexy.—Young [58] stated that he studied 8,000 cases of pulmonary tuberculosis as recorded in four great sanatoriums in Colorado. The records showed that the disease was arrested in about 67 per cent of the cases; if no genitourinary tuberculosis was present, the disease in about 72 per cent was arrested. Many of the patients went home apparently cured. Of those who had tuberculosis of the urogenital tract, a large percentage died. In fact, the largest percentage of deaths in tuberculosis sanatoriums, judging by the cases studied in Colorado,

58. Young, H., in discussion on Sargent, J. C.: Orchiopexy, J. Urol. **42**:860-862 (Nov.) 1939.

occurs among those patients who have the misfortune to have the genito-urinary tract involved by the process.

Young expressed regret that in recent years several writers have taught that radical operation is not necessary for early renal tuberculosis. He said that they have propounded the very dangerous doctrine: "If you get a very early case of tuberculosis of the kidney, don't operate. Sometimes these patients get well without operation." Young cited a case to show the fallacy of any such advice.

A patient who was wealthy, who was a sportsman with plenty of time and money and who could do whatever he wished came to Young suffering from extremely early tuberculosis of the left kidney. Young told the patient that he thought the kidney should be removed. That was a number of years ago, and injections of tuberculin were used considerably at that time. The patient had heard about this and said, "I live in Colorado. I can go to the best sanatoria or the best mountain resorts there; I can get the greatest experts to give me these injections of tuberculin." Young said he did not believe in this method, but the patient insisted that he wanted such treatment. He went to one of the greatest tuberculosis experts in the country. He received a full series of injections. Three years later he was brought back into the hospital on a stretcher and died in about two weeks. Necropsy was done. The left kidney was completely destroyed; the other kidney was involved, as were both seminal vesicles, both lobes of the prostate gland and both epididymides.

As to whether the epididymis, the seminal vesicle or the prostate gland is the initial focus, it does not make much difference. Certainly the seminal vesicles or the prostate gland show involvement in a very large percentage of cases. Young stated that he had a rude awakening a number of years ago, when he went over the cases in which he had treated patients by castration and later by epididymectomy. On very careful study of 175 cases he found that a large percentage of the patients were dead. They had died of tuberculosis of the prostate gland, seminal vesicles, kidney and lungs. That rude awakening caused him to investigate the problem of some form of treatment for tuberculosis of the deeper portion of the genital tract, and since then, he stated, whenever he has been able to show that tuberculosis of the seminal vesicles and the prostate gland, either or both, exists, he has operated. Young gives the opinion of himself and his staff, because a great many of the operations have been done by his associates and also by the residents, who have become very proficient in it. Their opinion is unanimous that they have saved many a life by radical surgical intervention.

In 27 per cent of those cases, in addition to taking out the entire seminal tract, that is, the epididymides, the vas, the vesicles and the

lobes of the prostate gland, Young has also taken out one kidney, and in a number of cases in which such extensive operations were done the patients were well at the time of his report.

EPIDIDYMIS

Tuberculosis.—Ormond and Meyers [59] reviewed a series of 35 cases in which "genital tuberculosis" has been proved by removal of the epididymis. This condition in itself is not very serious. Epididymectomy in the majority of cases is a satisfactory procedure, and orchidectomy is rarely necessary. Epididymectomy is not an emergency operation, and postponement of it until suppuration and rupture take place seems to do little harm.

In all cases every effort should be made to find and to eliminate, if possible, other forms of tuberculosis. Since tuberculous epididymitis is a symptom of more deeply seated tuberculosis elsewhere, the patient should whenever possible be treated like any other tuberculous subject, by means of rest, diet and care in a sanatorium.

The presence of Myco. tuberculosis in the urine practically always indicates renal tuberculosis.

The epididymis may be the primary site of infection in the genital tract.

In Ormond and Meyers' series, clinical tuberculosis of the urinary tract, although the most common concomitant infection, was not invariably present. Its incidence was a little more than 50 per cent. When clinical renal tuberculosis is present it is probable that the genital tract is infected from the urine through the prostate gland.

Prostatic massage does not seem to make much difference in cases of genital tuberculosis but is to be avoided.

Thomas,[60] in discussing Ormond and Meyers' paper, stated that during the seven years prior to the time of his discussion he had observed 97 patients who had some of the lesions of tuberculosis of the genitalia. Eighty-seven per cent of this group had tuberculosis situated elsewhere, and of this number 78 per cent had pulmonary tuberculosis. He stated the belief that tuberculosis of the genital tract is usually secondary to renal tuberculosis and that the primary urogenital infection spreads from the kidney downward.

In the 63 cases of tuberculosis of the genitalia that were adequately studied, 92 per cent of the patients had renal tuberculosis. Twenty-three patients suffering from genital tuberculosis came to necropsy, death being caused by pulmonary lesions, uremia and the like; all 23 patients

59. Ormond, J. K., and Meyers, K. L.: Tuberculous Epididymitis, J. Urol. **42**:829-842 (Nov.) 1939.

60. Thomas, G. J., in discussion on Ormond and Meyers,[59] p. 857.

of this group had definite renal tuberculosis. In view of these statistics, Thomas stated the belief that tuberculosis of the genital tract is more often associated with and secondary to lesions of tuberculosis in the kidney.

His evidence is not 100 per cent conclusive; however, he stated that these data suggest that the descending mode of invasion of the genital tract is most frequently via the urine. In his clinical experience the epididymis seems to be more frequently involved than the prostate gland, although data obtained from necropsies reveal that 22 of the 23 patients had tuberculosis of the prostate gland, while only 14 of the 23 had tuberculosis of the epididymis. In other words, the prostate gland is involved more often than are other genital organs.

Thomas showed a chart of data concerning the situation of the lesions in 200 cases of tuberculosis of the urogenital system. In 45 cases the lesions were situated in the prostate gland, in 40 in the bladder, in 16 in the epididymis, in 14 in the seminal vesicle, in 23 in the testes and in 13 in the epididymis and prostate gland. There were 3 cases of epididymal tuberculosis and 4 of tuberculosis of the seminal vesicle in which there was no gross evidence of prostatic tuberculosis. These were all gross observations. The kidney and prostate gland were not serially sectioned.

URINARY CALCULI

Chute [61] stated that urea-splitting bacteria are frequently found in association with and as the apparent cause of the formation of urinary calculi, especially recurrent and multiple calculi.

A review of all the cases of urinary stone in which the patients entered the Massachusetts General Hospital during 1937 showed that more than half had an infection with a urea-splitting organism as the only apparent cause. The commonest organism (60 per cent) was Bacillus proteus; next were nonhemolytic streptococci, staphylococci, Bacillus pyocyaneus, Bacillus influenzae and Micrococcus flavus, in that order of frequency.

In 80 per cent of cases of recurrent stone the patients were infected with urea-splitting bacteria, and in 60 per cent of cases of infection with urea-splitting bacteria the patients had multiple or recurrent stones. Thus, recurrent or multiple stones and such infections go hand in hand.

These infections, especially those caused by B. proteus, are often difficult to cure. They are almost never eradicated permanently until existing stones and also stasis have been removed. Chronicity of infection lessens the chance of permanent cure. The use of ammonium chloride as a urinary acidifier for infections of this type is contraindicated. Sulfanilamide has been the most effective drug.

61. Chute, R.: The Significance of Urea-Splitting Bacteria in the Formation of Urinary Calculi, New England J. Med. **219**:1030-1032 (Dec. 29) 1938.

HYPERTENSION

Mulholland [62] stated that there is a definite entity, involving the renal circulation at the renal artery, or else an inflammatory entity within the kidney itself, that produces an elevation of the blood vessel tone. This pathologic process can be determined and, if diagnosed, removed, with cure of the hypertension, as has been proved in experimental work and in clinical cases. Hypertension should be considered in the same light as a fever; it is a symptom rather than a disease. Every patient who has high blood pressure should be given treatment especially planned for him; that means that this treatment may be inadequate and ill advised unless the physician knows the status of the kidney. Mulholland stated the belief that urologists can cure an increasing number of patients with hypertension. Experimental work and clinical cases may explain the failure of many of the operations done on the nervous system for the relief of hypertension. Perhaps after performance of "lumbar sympathectomy" there are relief of the vascular spasm in the renal vessels and a temporary improvement in renal circulation. However, because of the vascular changes that have occurred there is a return to the condition present before operation; the blood pressure is similarly affected. Certainly, before any patient suffering from hypertension is subjected to any of the operative procedures now in favor for the relief of hypertension, the kidney should be ruled out as the possible cause of the hypertension. Surely, with all the evidence suggesting that the kidney may be the primary factor in initiating hypertension, the structure demands the careful and thoughtful attention of every urologist. It is a real challenge to the urologist to identify pyelonephritis in the stage in which pallor, underweight and slight albuminuria are the only signs. It is only by means of searching inquiry with the foregoing facts in mind that urologists will be adding more and more cases to the literature and also more patients who might otherwise have been doomed to a hypertensive end to the list of those in whom satisfactory results were obtained.

Crabtree and Prien [63] noted that there was evidence of damage to the arterial blood supply in most portions of a kidney in a case of severe bilateral postpartum pyelonephritis in which one kidney had been removed at the height of the infection and in which the other kidney apparently had recovered. Since these vessels are terminal, the injury from the initial infection should be expected to produce irreparable cortical damage in such kidneys.

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62. Mulholland, S. W.: Hypertension's Challenge to Urology, J. Urol. **42**: 957-968 (Dec.) 1939.

63. Crabtree, E. G., and Prien, E. L.: The Nature of Renal Injury in Acute and Chronic Colon Bacillus Pyelonephritis in Relation to Hypertension: A Combined Clinical and Pathological Study, J. Urol. **42**:982-995 (Dec.) 1939.

Clinical observation of 30 patients suffering from severe bilateral pyelonephritis during pregnancy from ten to eighteen years after the initial injury (the infection) showed that only 2 of these patients showed evidence of hypertension. When studies of renal function were made in the cases of 7 of these patients, all 7 exhibited severe degrees of renal injury.

Hypertension is not the rule in cases of severe injury to the kidneys referable to pyelonephritis occurring in pregnancy even remotely after the initial injury in patients who show reasonable degrees of health. This does not indicate whether these same patients may not be hypertensive nearer the end of life.

SURGICAL TREATMENT OF BLADDER, KIDNEY AND URETERS

Priestley [64] stated that during 1938 858 operations (exclusive of all transurethral procedures) were performed on 786 patients for various diseases of the genitourinary tract. There were 19 deaths in the hospital in the entire group of 786 patients, a mortality of 2.4 per cent.

During the three years prior to Priestley's report, the number of patients operated on for lesions of the kidney had increased steadily, and during 1938 there were 307 such patients. Approximately half (151) of these patients were operated on because of nephrolithiasis. Two deaths occurred in this group of 151 cases, a mortality of 1.3 per cent.

During 1938, 22 patients with stag-horn renal calculi were operated on, without mortality. In 18 cases the stones were unilateral, and nephrectomy was performed in 9 of these. In the remaining 9 cases a conservative operation was carried out, the stones being removed and the kidney preserved. In 4 cases bilateral stag-horn calculi were present, and bilateral conservative operations were performed in two stages. In no instance was secondary nephrectomy necessary.

The more widespread use of nephrostomy in selected cases has been of definite value. Nephrostomy not only permits the preservation of many severely damaged kidneys which otherwise might have had to be removed but reduces definitely the necessity for performance of emergency nephrectomy after various types of conservative operations on the kidney. During the past year nephrostomy was performed in approximately 30 per cent of the cases in which stones were removed from the kidney and in all cases in which nephrolithotomy was performed.

In 75 per cent of the 151 cases of nephrolithiasis in which the patients were operated on at the Mayo Clinic during 1938, conservative

64. Priestley, J. T.: Report of Urologic Surgery for 1938, Proc. Staff Meet., Mayo Clin. **15**:29-32 (Jan. 10) 1940.

operation was performed, that is, stones were removed and the kidney was preserved, and in only 25 per cent of cases was nephrectomy performed.

Fifty-two patients were operated on for hydronephrosis during 1938. On 31 (59.6 per cent) of these nephrectomy was performed, and on 21 (40.4 per cent) a conservative operation was performed. There were no deaths in this series, and secondary nephrectomy was not necessary in any case after conservative operation.

Nephrectomy was performed for renal tumors in 50 cases, with 2 deaths, and for renal tuberculosis in 20 cases, with 1 death. In 34 additional cases operations were performed for miscellaneous lesions of the kidney, with 1 death. A total of 307 patients underwent operations on the kidney during 1938, with 6 deaths, a mortality of about 2 per cent.

During 1938 ureterosigmoidostomy was performed in 13 cases, with 2 deaths. In 8 of these cases transplantation was performed as the preliminary stage to total cystectomy for carcinoma of the bladder. In this group of 8 cases the 2 deaths occurred.

Gradually, during recent years, as experience and efficiency with transurethral surgical procedures have increased, fewer and fewer suprapubic operations have been performed on the bladder. The first change in this regard was, of course, the introduction of transurethral prostatic resection. The added skill acquired by the urologist in carrying out this surgical procedure has enabled him to treat certain vesical lesions with equally satisfactory results. As a result, suprapubic operations on the bladder do not seem to be necessary as frequently as they were formerly. During 1938 the suprapubic approach was employed in the treatment of vesical neoplasm in 24 cases. Segmental resection for carcinoma of the bladder was carried out in 7 cases, without a death. Total cystectomy with preliminary transplantation of the ureters to the sigmoid was performed in 6 cases, with 1 death.

Operation was performed in 30 cases for cryptorchidism, the Meyer-Torek type of procedure being utilized most often. Results continue to be satisfactory after this operation for undescended testis. Operation was performed for hypospadias in 31 cases during 1938. The McIndoe operation, which has for its principle the use of an inlying tubular graft, has been giving increasingly satisfactory results in the surgical treatment of this condition.

TRANSURETHRAL OPERATIONS

Thompson [65] stated that a total of 4,073 patients were subjected to 7,656 transurethral operations in 1937 and 1938 at the Mayo Clinic. Since it is necessary in some instances to perform transurethral prostatic

65. Thompson, G. J.: Transurethral Surgery in 1937 and 1938, Proc. Staff Meet., Mayo Clin. **14**:657-661 (Oct. 18) 1939.

resection in more than one stage, 1,791 operative procedures were performed on 1,697 patients. Sixteen hundred and seven of these patients were operated on in one stage, 86 in two stages and 4 in three stages. Thus, in 94.7 per cent of cases transurethral resection in one stage sufficed. That transurethral resection has replaced other types of prostatectomy is evident from the fact that in only 2 cases was suprapubic enucleation done for benign hypertrophy during this period of two years. In 1 other case prostatectomy was done for sarcoma. It was necessary to perform cystostomy preliminary to transurethral resection in only 5 cases.

In not a single case during the two years was suprapubic cystostomy performed for the treatment of advanced renal insufficiency or for severe infection of the urinary tract. Thompson and his co-workers were able, by careful selection of methods, to carry on with drainage through a urethral catheter until transurethral resection was feasible. Success with this method of drainage hinges on vigilance and cleanliness in keeping open the proper type of urethral catheter, which has been carefully adjusted. It must be recognized, however, that some patients will not tolerate an inlying catheter and must be catheterized carefully at regular intervals until operation can be performed.

The mean average age of the patients during the two years was 66.2 years. There were 71 patients aged 80 years or more, and of these only 1 died, which seems to prove the relative safety of transurethral resection in comparison to other forms of prostatectomy.

The amount of tissue resected in the average case is interesting. If the small-bar type of prostate gland and contracted vesical neck are eliminated from consideration, it is found that the average amount removed during 1938 was 32.1 Gm. in each case.

In the large majority of cases less than one week of postoperative hospitalization was required, and of equal importance is the fact that only 25 patients of the total of 1,697 were in the hospital more than three weeks; of these, only 7 spent more than one month in the hospital after operation.

The mortality following transurethral prostatic resection during the two years was 1.6 per cent (27 deaths among the 1,697 patients).

Thompson's charts show that stones were removed from the ureter in 140 cases, a total of 199 manipulations being required. In the large majority of cases the stone was removed at the first attempt, being extracted from the ureter as a rule while the patient was on the cystoscopic table. There is no procedure in transurethral surgery which requires so much patience as the manipulation of a ureteral calculus.

After extracting a ureteral stone, Thompson wrote, he always places a ureteral catheter in the ureter and a urethral catheter in the bladder, so that for forty-eight hours all drainage of urine is mechanical, and the edematous ureter and trigon have time to recover from the trauma of manipulation.

Litholapaxy was performed in 142 cases. This, too, is a procedure which saves the patient many days in the hospital. During these two years, suprapubic lithotomy was performed only 11 times; this indicates that most vesical calculi can be removed without resorting to open operation.

The destruction of tumors of the bladder by transurethral fulguration was carried out in 374 instances. This includes those cases in which treatment by either transurethral or open operation in previous years had been followed by recurrence. For a number of patients presenting large papillary growths of low grade malignancy, the bulk of the tumor was removed by means of a cystoscopic forceps or resectoscope. Radon seeds were implanted in small tumors of a high grade of malignancy in 28 cases.

It is interesting that intravenous anesthesia was used in 1,882 cases. Since most of the procedures are of short duration, the intravenous injection of pentothal sodium (sodium-1-methylbutyl-thiobarbituric acid) by the fractional method is satisfactory. Thompson has found that transurethral prostatic resection can be performed in most cases in less than twenty minutes, and for patients aged 80 years or more who are in rather poor condition the intravenous method of producing anesthesia is far superior to other types; there is less bending and manipulation of the patient; he can sit up in bed a few hours after operation, and thus the chance of pulmonary and other complications is minimized. Spinal anesthesia was employed in 1,548 cases, with highly satisfactory results. Procaine hydrochloride injected through the fourth lumbar interspace in a dose of 80 mg. or less, depending on the weight and age of the patient, provides anesthesia for approximately one hour for transurethral prostatic resection or other intravesical manipulation. It seldom causes serious reactions. Inhalation anesthesia with nitrogen monoxide is the method of choice for infants and children and was used in 72 cases. Sacral block anesthesia was employed only 37 times because, in Thompson's opinion, severe physiologic reaction to the large amount of procaine hydrochloride which must be injected is observed frequently among men of an age at which prostatic disease is likely to occur. This chance for such a reaction to occur far outweighs any theoretic advantages which the method has over spinal anesthesia.

BACTERIOLOGY OF URINARY TRACT INFECTION

Schulte [66] studied the bacteriologic aspects of the urinary tract in normal persons and patients by inoculating 0.5 cc. of urine into dextrose–brain broth and hormone–blood agar pour plates. Subsequent identification of the organisms was made by using other mediums. For normal controls, only those persons were used who were not suffering from any clinical infection of the genitourinary tract and who, in addition, had negative smears in a Gram stain of the urinary sediment and prostatic secretion.

Schulte studied four groups of normal men. In the first, the second portion of the voided urine of a clean specimen was used. Small numbers of colonies of nine different organisms were found, of which micrococci, diphtheroids and Streptoccocus faecalis were most common. The second group, in which the urine was obtained by catheter, gave similar results, with fewer colonies. The third group, in which the urine was obtained as in the first group but after lavage of the anterior portion of the urethra, was divided into two equal subgroups, one having sterile urine, the other urine infected by Micrococcus. After voiding, prostatic massage was done. Culture of the secretion showed alpha streptococci in practically all cases and in those with micrococci in the voided specimen micrococci as well. Schulte concluded that micrococci are normal inhabitants of the anterior portion of the urethra and alpha streptococci of the posterior part of the urethra and the prostatic secretion.

Schulte also studied a fourth group, for which retrograde pyelograms were made. Urine obtained from the bladder cystoscopically gave the same results as have been recounted, but the results of examination of the urine from the renal pelvis were consistently negative. From this Schulte concluded that cystoscopic examination introduces bacteria from the urethra into the bladder. Schulte pointed out that this method of bacteriologic study will reveal those instances of clinical infection missed by Gram-staining of urinary sediment or of prostatic secretion. Staphylococcus aureus was never isolated from the urine or the prostatic secretion of normal subjects.

Schulte described a medium in which an organism's urea-splitting ability may be tested, using thymol blue as an indicator and quantitative determinations for ammonia. On this medium, Schulte found Proteus ammoniae and Micrococcus ureae to be the worst offenders. Str. faecalis did not utilize urea at all. Occasionally other organisms would split urea as much as would the aforementioned two. By culturing on this medium

66. Schulte, T. L.: Newer Methods in a Study of the Bacteriology of the Urinary Tract: Preliminary Report, Proc. Staff Meet., Mayo Clin. **14**:249-254 (April 19) 1939.

first it is possible to prevent overgrowth of other organisms and thereby make isolation more complete.

Schulte also checked the pathogenicity of gram-positive, mass-forming cocci in vivo on rabbits and guinea pigs and in vitro in human or horse serum. Correlation between the tests was 90 per cent. The coagulose test also differentiated the staphylococcus from the micrococcus.

Thompson and Schulte [67] described a medium on which the urea-splitting ability of an organism may be tested. The composition of the medium is peptone 0.2 per cent and sodium chloride 0.5 per cent in distilled water. To each liter 20 cc. of 0.2 per cent alcoholic solution of thymol blue is added. The p_H is then 6.8. The solution is sterilized in amounts of 10 cc. A solution of 10 per cent urea, sterilized by filtration, is added to the sterile tubes until the concentration of urea is 0.5 per cent. When the p_H reaches 9.4, the medium is deep blue. A positive reaction to this test is one in which this color is obtained within forty-eight hours, an experimentally determined standard. The blue color occurs when the level of free ammonia is not less than 25 mg. per hundred cubic centimeters. It was found best to use 0.5 cc. of urine as the inoculum. Three hundred specimens were studied; 200 were range finding and 100 for more intense study. Of these 100 specimens 24 were positive, yielding Proteus (13), diphtheroids (7), micrococci (2) and Salmonella morgani (2). In some cases the urea-splitting organism was detected only in this medium, and was not found when blood agar or eosin–methylene blue mediums were employed. Thompson and Schulte emphasized the importance of studying the urine for urea-splitting organisms in instances of (1) persistently alkaline urine, (2) acute diffuse fulminating hemorrhagic cystitis, (3) incrustations and (4) urinary calculi. Cases of acid urine and oxalate and urate stones were not involved, but in those cases in which alkaline urine and phosphate or carbonate calculi were present, more than 50 per cent had a urea-splitting organism present. Thompson and Schulte discussed some of the aspects of urea-splitting organisms which are of clinical importance. The present study constitutes a preliminary report. The importance of adding a few drops of urine to the urea broth is emphasized.

Crenshaw and Cook [68] pointed out the value of sulfanilamide in treating bacillurias (Escherichia coli, Aerobacter aerogenes, Salmonella, Proteus) of all sorts, especially those complicated by obstruction or chronic prostatitis. Mandelic acid therapy is still the best for use in cases of uncomplicated bacilluria. Neither sulfanilamide nor mandelic

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67. Thompson, L., and Schulte, T. L.: Urea-Splitting Organisms in Urine: Preliminary Report, Proc. Staff Meet., Mayo Clin. **14**:361-364 (June 7) 1939.

68. Crenshaw, J. L., and Cook, E. N.: Limitations, Dangers, and Failures of Sulfanilamide in the Treatment of Urinary Tract Infections, J. Urol. **41**:64-68 (Jan.) 1939.

acid is of much value in cases of nonspecific prostatitis. It is the best drug for a Proteus infection, but it is relatively inefficient in eradicating Str. faecalis and staphylococci. The micrococci fall into a variable intermediate group.

Crenshaw and Cook pointed out that dangers may be avoided by close supervision. Ten per cent of patients cannot take sulfanilamide. A high percentage have toxic symptoms, of which headache, malaise and weakness are the most common. Fever and cyanosis are indications for discontinuing the drug. Cyanosis portends methemoglobinemia or sulfhemoglobinemia as well as acute hemolytic anemia and granulocytopenia. Cutaneous reactions are of two types, increased sensitivity to light and a morbilliform rash. Two thousand patients suffering from urologic conditions received the drug, with only 3 severe reactions.

The dose was in most cases 40 grains (2.6 Gm.) daily for patients who had nongonorrheal conditions. In instances of gonorrhea, doses of 60 grains (4 Gm.) given daily for three or four days are followed by doses of 40 grains daily for seven days. In order to prevent a decrease in the carbon dioxide–combining power of the blood caused by sulfanilamide, Crenshaw and Cook advised administration of magnesium oxide, 1 or 2 grains (0.065 or 0.13 Gm.) with each tablet of the drug. The use of saline cathartics is forbidden. When sulfanilamide therapy or fever therapy alone fails in eradicating the gonococci, the two may succeed when combined. The para form of the drug is the most effective.

Thompson [69] pointed out the unsatisfactory management of patients who have an obstructing enlarged prostate gland in the presence of chronic renal insufficiency prior to the introduction of transurethral surgical procedures. The treatment of patients with such a condition was prolonged and disappointing, and it occasionally ended without surgical treatment other than permanent suprapubic drainage. With careful preoperative and postoperative care, such patients now achieve complete relief quickly by means of transurethral resection. Thompson's illustrative case was one in which a man 52 years of age had had symptoms of prostatic obstruction for two years and loss of strength, drowsiness and vomiting for two months. On admission he was dehydrated, anemic and underweight (loss of 40 pounds, or 18 Kg.) and had mild convulsions and Kussmaul's breathing. The bladder extended to the umbilicus. The prostate gland was only moderately enlarged on rectal examination. Treatment consisted of installation of an inlying urethral catheter and parenteral administration of fluids (5 per cent dextrose in physiologic solution of sodium chloride, lactate-Ringer [Hartmann's] solution

69. Thompson, G. J.: Transurethral Resection in the Presence of Marked Renal Insufficiency: Report of Case, Proc. Staff Meet., Mayo Clin. **14**:401-404 (June 28) 1939.

and 5 per cent solution of sodium bicarbonate) daily. By means of this treatment the value for urea in the blood, which on admission had been 488 mg. per hundred cubic centimeters, was reduced to 124 mg. on the day of operation, twenty-three days after admission. The carbon dioxide–combining power had been 12.6 volumes per cent on admission, and this was satisfactorily controlled. With intravenous anesthesia produced by pentothal sodium (sodium-1-methylbutyl-thiobarbituric acid) 19 Gm. of prostatic tissue was removed by transurethral resection. Convalescence was uneventful. Postoperative examination showed no residual urine; there had been 650 cc. on the patient's admission. The value for blood urea when a determination was last made was 104 mg. per hundred cubic centimeters. The patient's symptoms and general health had improved markedly at the time of Thompson's writing. Patients previously and similarly treated have, as a group, shown improvement in their general health.

Sandholzer and Scott [70] presented the results of a study of the aerobic gram-negative bacilli encountered in infections of the genitourinary tract. In all, 530 cultures of material from 283 patients were subjected to detailed investigation with the aim of ascertaining whether any relation between the type of organism present and the response of the patient to treatment could be discovered.

The bacteria consisted of six genera. Members of Escherichia were found in 83 per cent of the cultures (27 species or types) and members of Aerobacter in 13 per cent (14 species or types), whereas the remaining 4 per cent were distributed among the genera Salmonella, Proteus, Shigella and Pseudomonas.

Hemolytic activity was determined on rabbit's blood-pork infusion agar in pour plates. Although all of Brown's types of hemolysis were observed, the type was independent of the genus or species of the organisms present.

When specimens of urine from the same subjects were cultured at intervals over a period of months, the type of organism recovered in some instances remained constant as to species and type of hemolysis, but in other instances variations in either one or both of these factors occurred. Thus, from 1 patient nine different species belonging to three genera were recovered at various times.

Correlation of the bacteriologic observations with the clinical records suggests that differences in the therapeutic response of patients who have bacillary infections of the urogenital tract may depend to some degree on the particular type of gram-negative bacillus responsible for the infection.

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70. Sandholzer, L. A., and Scott, W. W.: A Bacteriological and Clinical Study of Bacillary Infections of the Urogenital Tract, J. Urol. **42**:183-196 (Aug.) 1939.

HERNIA AND INFECTION OF THE URINARY TRACT

Seaman [71] stated that the predisposing cause of hernia is the persistence of the vaginal process, which accompanies the testicle in its descent into the scrotum. It rarely causes pain, even when it exists.

Pain in the groin and epididymis referable to prostatovesiculitis frequently is mistaken for evidence of hernia.

Performance of herniorrhaphy for pain alone is never justifiable.

Infection in the lower portion of the urogenital tract is often hidden.

The "injection" method of treating patients who have pain but no hernia should not be condoned.

Pain following herniorrhaphy is frequently the result of vasitis and not of nerves being caught in the line of sutures.

Mandelic acid and sulfanilamide are two great adjuvants in the treatment of prostatovesiculitis.

Leukorrhea has not been stressed sufficiently as a cause of prostatovesiculitis.

Cases involving the aforementioned conditions will not be adequately adjudicated in the courtroom until the diagnosis in all instances has been made properly.

UROGRAPHY

Crane [72] reported a case in which sudden death occurred following intravenous administration of diodrast (3,5-diiodo-4-pyridone-N-acetic acid and diethanolamine). Thirty cubic centimeters was injected in the usual manner during about two minutes. After this, the patient became cyanotic, and his respirations decreased to 6 per minute. Death occurred about twenty minutes later in spite of the use of the usual restoratives. The cause of death as indicated by necropsy was edema of the lungs and of the larynx. A small number of cases of this type have been reported in the literature. In most of them, as in Crane's case, the patients were very ill.

Wesson,[73] in discussing the case reported by Crane in which death followed the intravenous administration of diodrast for intravenous urographic study, cited the work of Robb and Steinberg, who used large amounts of the medium injected very rapidly for the purpose of showing the outline of the heart. These investigators have used this technic in 456 cases, without the occurrence of a single death.

In a discussion of urography, Braasch [74] stated that at the Mayo Clinic excretory urographic methods have been employed for approximately 25,000 patients, without occurrence of a death.

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71. Seaman, J. A.: Hernia and Lower Urological Tract Infection, J. Urol. **42**: 887-892 (Nov.) 1939.

72. Crane, J. J.: Sudden Death Following Intravenous Administration of Diodrast for Intravenous Urography, J. Urol. **42**:745-748 (Nov.) 1939.

73. Wesson, M. B., in discussion on Crane,[72] p. 754.

74. Braasch, W. F., in discussion on Crane,[72] p. 757.

Nesbit and Douglas [75] stated that the subcutaneous administration of adult doses of diodrast in proper dilution with physiologic solution of sodium chloride is entirely safe and technically advantageous. No ill effects, either local or systemic, were noted in any of their cases.

The solution is absorbed completely in forty-five to sixty minutes. Optimal excretion of the dye in the normal kidney occurs in ten to thirty minutes after injection.

This method has an advantage over intravenous pyelographic methods for infants in its ease of administration as well as in the higher incidence of diagnostic roentgenograms thereby obtained.

Schulte and Emmett [76] reviewed urographic studies made in 112 cases of retroperitoneal extrarenal tumor, proved at operation, hoping to find some diagnostic characteristics in the urograms. The 112 cases may be divided into two groups: (1) 40 cases in which the retroperitoneal tumor did not originate in the pancreas or kidney and (2) 72 cases in which the tumor originated in the pancreas. In 29 (72.5 per cent) of the first group of cases, examination of the urograms disclosed displacement of the kidney or the ureter or both. In these cases the displacement was very evident; the kidney and ureter most often were definitely displaced medially or laterally. In a few cases, however, the kidney was displaced upward or downward, and there occasionally was evidence of bizarre types of renal rotation in various planes. In 68 (94.4 per cent) of the 72 cases in group 2 there was no displacement of the kidney or ureter. Histopathologic examination revealed that most of the tumors in the cases of group 1 were sarcomas, whereas in the cases in group 2 approximately two thirds of the tumors were adenocarcinomas, and a third were cysts.

TESTOSTERONE PROPIONATE

McCullagh and McGurl [77] stated that complete sexual maturity can be developed in instances of severe testicular deficiency by injection of testosterone propionate. The attainment of normality in some features, such as beard and prostatic growth, requires larger doses and a considerably longer time than is required for the response of other structures.

Testicular descent has occurred in 3 of 10 cases, and the testes have increased in size, as judged by palpation, in 2 cases. Skeletal maturation

75. Nesbit, R. M., and Douglas, D. B.: The Subcutaneous Administration of Diodrast for Pyelograms in Infants, J. Urol. **42**:709-712 (Nov.) 1939.

76. Schulte, T. L., and Emmett, J. L.: Urography in the Differential Diagnosis of Retroperitoneal Tumors, J. Urol. **42**:215-219 (Aug.) 1939.

77. McCullagh, E. P., and McGurl, F. J.: Observations on the Clinical Use of Testosterone Propionate, J. Urol. **42**:1265-1273 (Dec.) 1939.

in hypogonadal men receiving doses varying approximately from 75 to 150 mg. per week may advance at a rate exceeding the normal.

Injections of testosterone propionate cause a pubertal type of acne.

A case is described in which repeated examinations of the semen showed the total production of sperm to decrease markedly during therapy. There was an apparent though less definite decrease in the motility of spermatozoa and in the volume of the semen.

Results of testosterone propionate therapy in 4 cases of gynecomastia are reported, with comments on this therapy for 14 women, in 2 of whom treatment produced evidences of virilism.

HEMATURIA

Barach and Pennock [78] stated that the orthotolidine test is a sensitive method of determination of occult hematuria. A positive reaction to this test was obtained in one third of 681 general cases of the so-called chronic diseases in which treatment was medical. Occult bleeding is less common in youth, when there are more intact vessels, and it is more common in females than in males, because of the greater source of bleeding in the female generative tract. Seasonal variation pointed to the highest incidence during the summer months. Albuminuria and occult blood are found independently of each other, each having its own significance. Glycosuria is not a cause of occult bleeding. Arsenicals in therapeutic doses do not cause occult bleeding. Alkalinity or acidity of the urine is not a cause of occult bleeding. In patients showing persistent occult hematuria, hypochromic anemia is common. A review of the type of case in which the strongest reactions occurred reveals that these reactions were most pronounced in the clinically recognized serious types of disease and that the test reflects the patient's actual condition.

ANURIA

Kutzmann [79] stated that anuria is a serious clinical condition and therefore is of great importance.

Anuria may be of either the prerenal or the renal secretory type or of the postrenal, or obstructive, type. With the former the causative factors are either proximal to or are in the kidney itself, whereas with the latter the cause lies in or distal to the renal pelvis.

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78. Barach, J. H., and Pennock, L. L.: Diagnostic Value of Occult Hematuria: A Study of Three Thousand Specimens of Urinary Sediment, J. A. M. A. **114**: 640-642 (Feb. 24) 1940.

79. Kutzmann, A. A.: Anuria: A Clinical Study, J. Urol. **42**:1274-1299 (Dec.) 1939.

There are many etiologic factors in anuria, but they may conveniently be grouped into (1) prerenal, (2) renal, (3) postrenal—intrinsic and extrinsic—and (4) a transitional or combination group.

Clinically, a patient who has anuria may be considered as being in the period of tolerance when no signs or symptoms except the anuria are noted; as being in a period of minor intolerance when mild nausea, vomiting hiccup, headache, and diarrhea are noted, and as being in a period of major intolerance when the given signs and symptoms progress to convulsions and coma and finally to death.

The diagnosis of anuria is made from a carefully taken history, physical examination, absence of urinary secretion, plain roentgen study, ureteral catheterization and studies of the blood chemistry.

Treatment consists of an immediate diagnosis as to the type of anuria, supportive treatment for the secretory type and immediate drainage either by ureteral catheterization or operation for the postrenal or obstructive type, supported by the usual administration of fluids. Surgical intervention may be indicated in any well selected case of anuria. The prognosis is much better for the obstructive type than for the secretory type of anuria.

Five personal cases of anuria are presented: (1) a case of nephritis in which there was anuria of eighteen days' duration and in which there was a level of 300 mg. of nonprotein nitrogen and 24 mg. of creatinine per hundred cubic centimeters of blood; (2) a case in which postrenal reflex anuria followed ureteral catheterization; (3) a case in which secretory anuria was caused by necrosis of the tubular epithelium following cholecystectomy and was associated with acute hemorrhagic pancreatitis; (4) a case in which postrenal or obstructive anuria was referable to a calculus situated in the ureter of a remaining kidney, and (5) a case in which postrenal and renal secretory anuria was associated with a value for nonprotein nitrogen of 267 mg. and a value for creatinine of 40 mg. per hundred cubic centimeters of blood; in this case the condition was caused by an extrinsic bilateral ureteral obstruction due to diffuse retroperitoneal carcinomatosis.

RENAL DIGESTIVE REFLEX

Emerson, Smith and Orkin [80] stated that an analysis of 487 consecutive cases of disease of the upper part of the urinary tract showed that in 50 (10.2 per cent) a diagnosis of lesion of the digestive tract had been made and that the average duration of symptoms referable to the gastrointestinal and urogenital tracts was four years and one and nine-

80. Smith, E., and Orkin, L.: The Renal Digestive Reflex, J. Urol. **43**:1-17 (Jan.) 1940.

tenths years respectively. There was no case in which the urogenital complaints preceded the gastrointestinal symptoms.

Twenty-three patients had undergone a previous abdominal operation, without benefit. In this group 20 had never had any urogenital symptoms prior to, and 10 never had any urogenital symptoms before or after, abdominal operation.

The authors demonstrated the reflex nervous mechanism by means of which a diseased kidney may cause symptoms in the digestive tract. This mechanism also explains the reason that a urinary lesion on one side may give rise to symptoms in the digestive tract on the other side, of which condition 6 cases are reported.

From a consideration of all observations, they suggested that for any patient who has undergone previous abdominal surgical exploration with no relief of symptoms or any patient in whose case the history and the results of physical and gastrointestinal laboratory examination do not dovetail urologic investigation should be done.

ANESTHETIC AGENTS

Tuohy and Thompson [81] recommended solutions of 2 per cent cocaine, 4 per cent metycaine or 1 per cent diothane (but not procaine) locally for simple procedures. When the surgeon is dealing with apprehensive or hypersensitive patients, the intravenous administration of pentothal sodium (sodium-1-methylbutyl-thiobarbituric acid) may be advisable. The advantages of this type of anesthesia are easy induction and a short recovery period and the noninflammable nature of the agent. It therefore has replaced anesthesia produced by inhalation anesthetic agents to a large degree, especially for elderly, hypertensive or debilitated patients and in procedures in which considerable electrical equipment is used. Rectal anesthesia (avertin with amylene hydrate) is used only occasionally, because of its depressing effect on the systolic blood pressure.

For transurethral prostatectomy, Tuohy and Thompson outlined a course of premedication. For the sturdier patients, low spinal anesthesia may be produced by a moderate dose. The importance of preventing vascular collapse by using the interspace of the fourth and fifth lumbar vertebrae is emphasized. Ephedrine sulfate (3/8 grain, or 0.024 Gm.) is used routinely in the production of local anesthesia at the site of the lumbar puncture except in cases of hypertension. If the pressure decreases subsequently, ephedrine sulfate administered intravenously helps to maintain the vascular tone.

81. Tuohy, E. B., and Thompson, G. J.: Methods of Anesthesia for Transurethral Prostatic Resection and Other Cystoscopic Procedures, J. Urol. **42**:642-649 (Oct.) 1939.

For Tuohy and Thompson, intravenous anesthesia was the method of choice in approximately 50 per cent of 3,480 procedures performed on the lower part of the genitourinary tract. Most of the remainder were done under spinal, block or local anesthesia. Tuohy and Thompson reported in some detail their method of producing anesthesia intravenously. Fractional administration of a 2.5 per cent solution of pentothal sodium is used. Ephedrine sulfate, oxygen and parenteral fluids are given on the operating table as indicated.

Dr. J. M. T. Finney, Dr. Dean Lewis and Dr. Harvey Cushing. The photograph was taken by Dr. J. Murray Washburn, of Lake Lure, N. C., on the occasion of the testimonial dinner given in Baltimore for Dr. Lewis in 1926.